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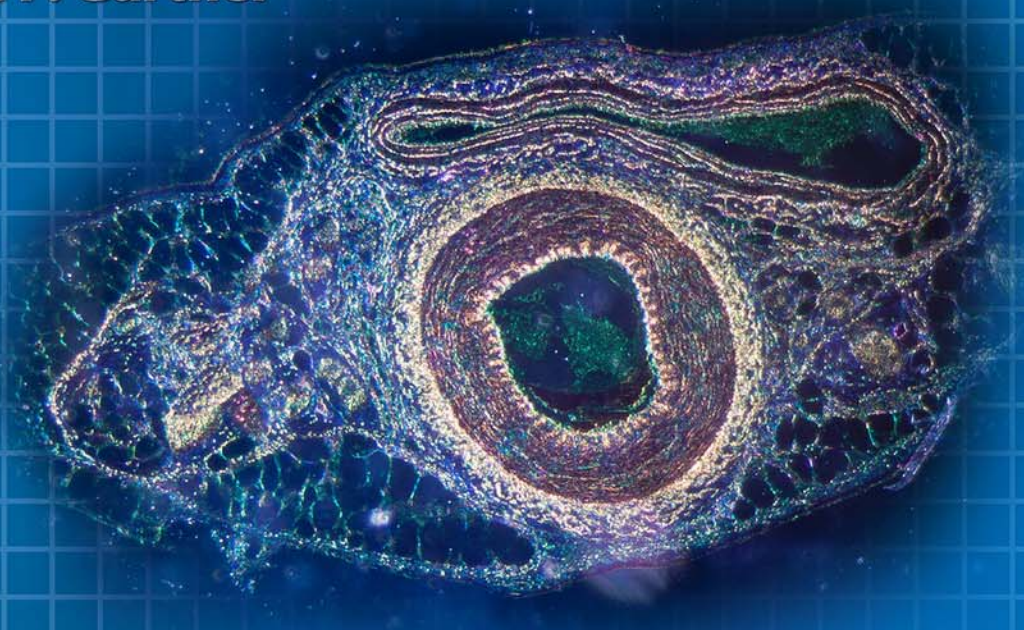
Cell Biology & Histology

EIGHTH EDITION

Leslie P. Gartner



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Leslie P. Gartner, PhD
Professor of Anatomy (Retired)
Department of Biomedical Sciences
University of Maryland Dental School
Baltimore, Maryland

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To my wife, Roseann,
my daughter, Jen,
and my mother, Mary
L.P.G.

Although it has been stated that writing is a lonely profession,
I have been very fortunate in having the company of my faithful
Airedale Terrier, Skye, who, as is evident in the accompanying photograph,
kept me company as I was sitting at my computer.

Preface

I am very pleased with the reception of the previous editions of this book as well as with the many favorable comments from students who used it in preparation for USMLE Step 1 or as an outline and study guide for their histology and/or cell biology courses in professional schools or undergraduate colleges.

Many of the chapters have been extensively revised and updated to incorporate current information, and the content of the text was revised to present material emphasized on National Board Examinations as succinctly as possible while still retaining the emphasis on the relationship between cell structure and function through the vehicle of cell and molecular biology. A tremendous amount of material has been compressed into a concise but highly comprehensive presentation, using many new and some revised illustrations. The relevancy of cell biology and histology to clinical practice is illustrated by the presence of clinical considerations within each chapter, as appropriate.

The greatest changes that occurred in the evolution of this book from its previous edition are the addition of many clinical considerations as well as tabular information. Moreover, almost all of the chapter questions and Comprehensive Examination questions have been revised to mirror the format of the questions in USMLE Step 1. I hope that these changes make this board review book more interesting and pertinent, and the presentation of material in tables conserves time in the review process for medical students in their preparation for USMLE Step 1.

I am sad to announce that Jim Hiatt, my coauthor throughout the first seven editions of this review book, decided to complete his retirement from the faculty of the University of Maryland School of Dentistry by withdrawing his participation in the preparation of the current edition of this textbook. Jim and I have collaborated in many aspects of our professional careers. We taught anatomy together; published numerous research articles together; and, counting new editions, authored 22 textbooks together. Although our professional collaboration has regretfully ended, our friendship remains as strong as ever.

As always, comments, suggestions, and constructive criticism of this book are welcome. Please address all comments to LPG21136@yahoo.com

Leslie P. Gartner

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I am grateful to the following individuals for their help and support during the preparation of this book: Crystal Taylor, my ever wonderful Acquisitions Editor who shepherded this and many of my previous textbooks through the various Publications Committees; Lauren Pecarich, Editorial Coordinator, who oversaw chapter by chapter the collection of the manuscript; Andrea Vosburgh, who was responsible for the development and content; Jennifer Clements, Art Director, who expertly handled the art program; and especially Kelly Horvath, my always helpful Freelance Editor, who made sure that everything was consistent throughout the chapters and that the tables and figures, despite their occasional recalcitrant behaviors, maintained their proper numerical orders.

I would also like to thank Dr. Lisa M. J. Lee, Associate Professor, Department of Cell and Developmental Biology, University of Colorado School of Medicine, Aurora, Colorado, for reading the entire manuscript and making valuable suggestions to improve the final quality of this eighth edition.

Finally, I would like to thank my family again for encouraging me during the preparation of this work. Their support always makes the writing an achievement.

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chapter 1

Cell

I. THE CELL

The basic living component of the human body is the cell. Although at least 200 different cell types constitute the body, each with unique functions, certain fundamental features are present in most cells, and this chapter will concentrate on the description of those elements in common. Every cell has a **cell membrane** (also known as **plasma membrane**, **plasmalemma**) that surrounds it and maintains its integrity. The material surrounded by the cell membrane, known as the **protoplasm**, is divided into two components, the **cytoplasm** and the **nucleoplasm**. The cytoplasm has structural components and a fluid component. The structural components are of three types: **organelles**, **inclusions**, and the **cytoskeleton**, which are suspended in the fluid component, the **cytosol**, composed mostly of water enriched by dissolved/suspended inorganic and organic constituents. The nucleoplasm is housed in the **nuclear envelope**–bound **nucleus**, whereas the cytoplasm is located between the cell membrane and the nuclear envelope. The interactions among certain organelles result in the uptake and release of material by the cell, protein synthesis, and intracellular digestion, among other functions.

The organelles are the metabolically active units of the cell. With the exception of the cell membrane, which surrounds the cytoplasm, all other organelles are suspended within the cytoplasm.

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II. OVERVIEW—CELL MEMBRANE

A. Structure. The cell membrane (also known as the **plasma membrane** or **plasmalemma**) is approximately 7.5 nm thick and consists of an inner and an outer leaflet, known as the **phospholipid bilayer**, and its **integral** and **peripheral proteins**.

1. The **inner leaflet** faces the cytoplasm, and the **outer leaflet** contacts the extracellular environment.
2. Viewed by transmission electron microscopy (TEM), the cell membrane displays a trilaminar structure, referred to as the **unit membrane**.

B. Function

1. The cell membrane maintains the cell's structural and functional integrity.
2. It acts as a **semipermeable** membrane, restricting movement of material between the cytoplasm and the external environment.
3. It assists in the recognition of macromolecules and other cells as well as allows the cell to be recognized by other cells; it also controls interaction between cells.
4. It assists in the transduction of extracellular signals into intracellular events.
5. It maintains a potential difference between the cytoplasmic and extracellular sides.

III. CELL MEMBRANE FLUID MOSAIC MODEL

A. The phospholipid bilayer, composed of phospholipids, glycolipids, and cholesterol (Figs. 1.1 to 1.3), is freely permeable to small, lipid-soluble, nonpolar molecules but is impermeable to charged ions.

1. The various types of **phospholipids**, the major component of the phospholipid bilayers, are **amphipathic** molecules, consisting of a **polar** (**hydrophilic**) head and two **nonpolar** (**hydrophobic**) fatty acid (acyl) tails, one of which is usually unsaturated. Phospholipid distribution is asymmetrical in the two leaflets.
   a. The **polar head** of each molecule faces the membrane surface, whereas the **tails** project into the interior of the membrane, so they face each other (see Fig. 1.1).
   b. The leaflet **tails** are mostly 16 to 18 carbon chain fatty acids, and they form weak **noncovalent** bonds that attach the two leaflets to each other.

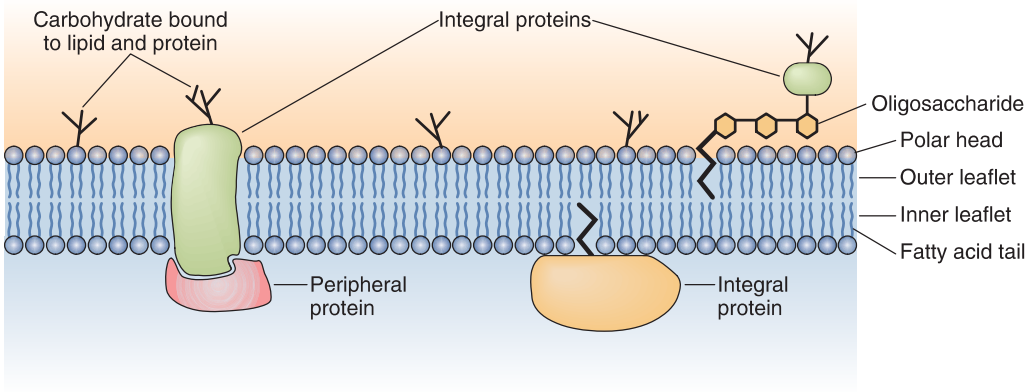


FIGURE 1.1. The cell membrane showing the outer (*top*) and inner (*bottom*) leaflets of the unit membrane. The hydrophobic fatty acid tails and the polar heads of the phospholipids constitute the phospholipid bilayer. Integral proteins are embedded in the phospholipid bilayer. Peripheral proteins are located primarily on the cytoplasmic aspect of the inner leaflet and are attached by noncovalent interactions to integral proteins.

FIGURE 1.2. Photomicrograph of a collecting duct of the kidney displaying tall columnar cells. The *arrows* indicate the cell membranes where two cells contact each other (×1,323).

FIGURE 1.3. Transmission electron micrograph of the basal region of a columnar cell from a mouse kidney collecting tubule. The basal cell membrane forms numerous complex folds (*arrowheads*) to increase the surface area of the cell. M, mitochondria; *arrow*, basal lamina (×28,435).

2. **Glycolipids** are restricted to the extracellular aspect of the outer leaflet. **Polar carbohydrate residues** of glycolipids extend from the outer leaflet into the extracellular space and form part of the **glycocalyx**.
3. **Cholesterol**, only 2% of plasmalemma lipids, is present in both leaflets and helps maintain the structural integrity of the membrane. **Fluidity increases** with increased temperature and with decreased saturation of the fatty acid tails and **decreases** with an increase in the membrane's cholesterol content.
4. Microdomains of the cell membrane, known as **lipid rafts**, are regions of the membrane with greater concentration of **cholesterol** and **glycosphingolipids**. Lipid rafts are thicker and less fluidic than the surrounding cell membrane. Some of these lipid rafts have integral and peripheral proteins associated with them that function in **cell signaling**. Individual lipid rafts may specialize in particular signaling processes by sustaining the three-dimensional relationship between the receptor and the signaling molecule, thereby facilitating their interaction.

B. Membrane proteins (see Fig. 1.1) are of two types: *integral proteins* and *peripheral proteins*; in most cells, they constitute ~50% of the plasma membrane composition, although in some instances, as in myelin, the ratio can be as little as 25%. Some membrane proteins **diffuse laterally** in the phospholipid bilayer; others are **immobile** and are held in place by cytoskeletal components.

1. **Integral proteins** are embedded in the phospholipid bilayer.
   a. **Transmembrane proteins**, composed mostly of **glycoproteins**, span the entire cell membrane thickness and **may** function as/in **membrane receptors**, **enzymes**, **cell adhesion molecules**, **cell recognition proteins**, **signal transduction**, and **transport proteins** (Table 1.1).
      (1) Transmembrane proteins are **amphipathic**, with some **hydrophilic** and **hydrophobic** amino acids that interact with the hydrocarbon tails of the membrane phospholipids.
      (2) Most transmembrane proteins are **multipass proteins**: they are folded in such a fashion that they pass back and forth across the plasmalemma several times.
   b. Integral proteins can be anchored to the inner (or occasionally outer) leaflet via fatty acyl or prenyl groups.
   c. In freeze-fracture preparations, integral proteins remain preferentially attached to the **P-face**, the outer (**p**rotoplasmic face) surface of the inner leaflet, rather than to the **E-face** (**e**xtracellular face; Fig. 1.4).

table 1.1 Major Classes of Membrane Proteins

Major Class	Functions
Receptor protein	Recognizes and binds signaling molecule on the extracellular surface of the cell membrane
Enzyme	Functions differ depending on the enzyme (e.g., energy utilization and digestion)
Pump	Transports ions and small molecules across the cell membrane by the expenditure of energy
Channel	Transports ions and small molecules across the cell membrane without the expenditure of energy
Linker protein	Functions in the attachment of the cell to the extracellular matrix
Structural protein	Functions in attaching neighboring cells to each other

2. **Peripheral proteins** are located either on the cytoplasmic or on the extracellular aspects of the cell membrane but do not enter the phospholipid bilayer.
   - **a.** Covalently linked glycolipids on the external aspect of the plasmalemma act as anchors for peripheral proteins, which then extend into the extracellular space.
   - **b.** Commonly, carbohydrates may bind to the peripheral proteins located on the extracellular aspect of the plasmalemma, forming **glycoproteins**.
   - **c.** Peripheral proteins may also bind to the phospholipid polar groups or integral proteins of the membrane via noncovalent interactions; in this case, they function as **electron carriers** (e.g., cytochrome c), as part of the **cytoskeleton**, or as part of an **intracellular second messenger system**.
   - **d.** Among these peripheral proteins are a group of anionic, calcium-dependent, lipid-binding proteins known as **annexins**, which act to modify the relationships of other peripheral proteins with the phospholipid bilayer and also to function in membrane trafficking and the formation of ion channels; **synapsin I**, which binds synaptic vesicles to the cytoskeleton; and **spectrin**, which stabilizes cell membranes of erythrocytes.

CLINICAL CONSIDERATIONS

A family of transmembrane proteins located on the surface of cells, including immune cells, that bind to the sugar sialic acid is known as **Siglecs** (sialic acid–binding immunoglobulin-type lectins). Sialic acid is located on most mammalian cells and signals to immune cells that the cells it occupies are "self" and should not be killed. Immune cells, such as natural killer cells, whose Siglecs bind to sialic acid, become inhibited and do not kill the cell that they contacted. Certain cancer cells take advantage of this phenomenon by placing many sialic acid residues on their surface, thus eluding attack by immune cells.

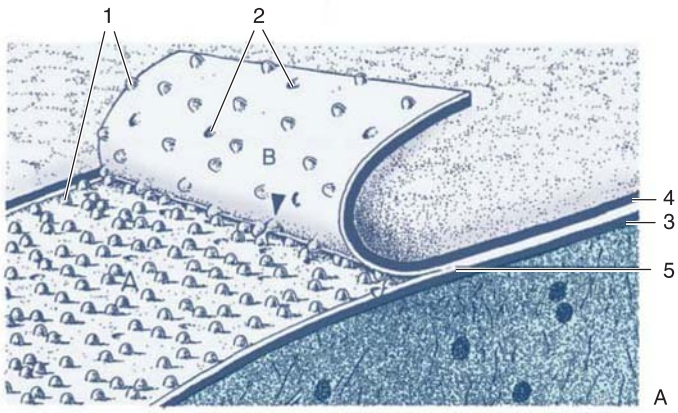


FIGURE 1.4. Freeze-fracturing cleaves the cell membrane (5). The impressions (2) of the transmembrane proteins are evident on the E-face between the inner (3) and outer leaflets (4). The integral proteins (1) remain preferentially attached to the P-face **(A)**, the external surface of the inner leaflet; fewer proteins remain associated with the E-face **(B)**, the internal surface of the outer leaflet. The *arrowhead* indicates a transmembrane protein attached to both E-face and P-face. (Reprinted with permission from Krstic RV. *Ultrastruktur der Saugertierzelle*. Berlin, Germany: Springer Verlag; 1976:177.)

C. **Glycocalyx (cell coat), located on the outer surface of the outer leaflet of the plasmalemma, varies in appearance (fuzziness) and thickness (up to 50 nm).**
   1. It consists of polar oligosaccharide side chains as well as **proteoglycans**. The oligosaccharides are linked covalently to most proteins and some lipids (glycolipids) of the plasmalemma.
   2. **Functions**
      a. The glycocalyx aids in **attachment** of some cells (e.g., fibroblasts but not epithelial cells) to extracellular matrix components.
      b. It **binds** antigens and enzymes to the cell surface.
      c. It facilitates **cell–cell recognition** and **interaction**.
      d. It **protects cells** from injury by preventing contact with inappropriate substances.
      e. It assists T cells and antigen-presenting cells in **aligning** with each other in the proper fashion and aids in preventing inappropriate enzymatic cleavage of receptors and ligands.
      f. It lines (in blood vessels) the endothelial surface to decrease frictional forces as the blood rushes by, diminishes loss of fluid from the vessel, and inhibits coagulation.

IV. CELL MEMBRANE TRANSPORT PROCESSES

These processes include transport of a single molecule (**uniport**) or cotransport of two different molecules in the same (**symport**) or opposite (**antiport**) direction.

A. **Passive transport (Fig. 1.5) includes *simple* and *facilitated diffusion*.** Neither of these processes requires energy because molecules move across the cell membrane **down a concentration or electrochemical gradient**.
   1. **Simple diffusion** is the transport of small nonpolar molecules (e.g., O_2 and N_2) and small, uncharged polar molecules (e.g., H_2O, CO_2, and glycerol) directly across the cell membrane without the need for ion channels or carrier proteins. It exhibits little specificity for the transported molecule, and the diffusion rate is proportional to the concentration gradient of the diffusing molecule.
   2. **Facilitated diffusion** occurs via **ion channels** and/or **carrier proteins**, structures that exhibit **specificity** for the transported molecules. Not only is it faster than simple diffusion, but it is also responsible for providing a pathway for ions and large polar molecules to traverse membranes that would otherwise be impermeable to them.
      a. **Ion channel proteins** are multipass transmembrane proteins that form small aqueous pores designed to permit specific small water-soluble molecules and ions, such as Cl^-, to pass down an electrochemical gradient (**passive transport**).
      b. **Aquaporins** are channels designed for the rapid transport of water across the cell membrane without permitting an accompanying flow of protons to pass through the channels. Aquaporins

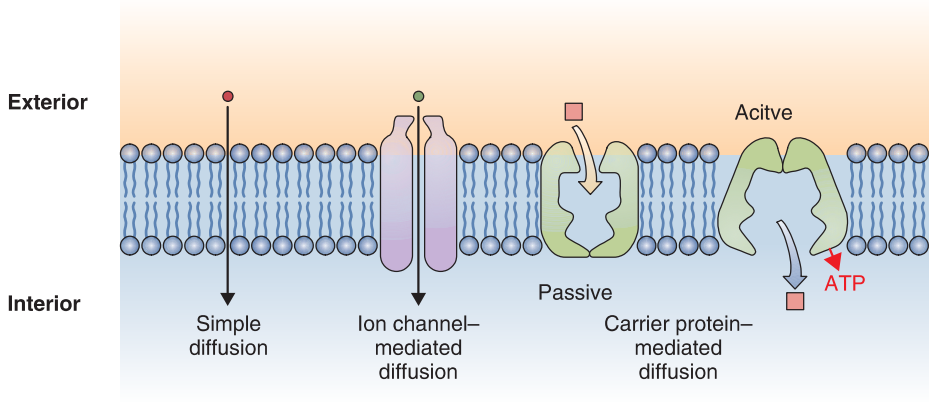


FIGURE 1.5. Passive transport of molecules across cell membranes by simple diffusion (*left*) and by either of the two types of facilitated diffusion mediated by ion channel proteins (*center*) and carrier proteins (*right*).

force water molecules to flip-flop halfway down the channel, so that water molecules enter with their oxygen leading into the channel and leave with their oxygen trailing the hydrogen atoms.

c. **Carrier proteins** are multipass transmembrane proteins that undergo reversible conformational changes to transport specific molecules across the membrane; these proteins function in both passive transport and **active transport**.

CLINICAL CONSIDERATIONS

Cystinuria is a hereditary condition caused by abnormal carrier proteins that are unable to remove cystine from the urine, resulting in the formation of kidney stones.

Cystic fibrosis is a hereditary disease involving a mutation in the **cystic fibrosis transmembrane conductance regulator gene** that causes the manufacture of malformed **chloride channel proteins** that are unable to transport chloride ions, causing an increase in the entry of Na^+ ions into the cell. The higher intracellular concentration of NaCl causes the increased flow of water into the cell, and the mucin that is released into the extracellular environment becomes thick mucus because of dehydration. The thick mucus obstructs the very small bronchiolar passageways of the lungs, and, as the disease progresses, infections result, the lungs become unable to function properly, and the individual succumbs to the disease.

B. Active transport is an *energy-requiring process* that transports a molecule *against* an electrochemical gradient via *carrier proteins*.

1. **Na^+-K^+ pump** is a carrier protein that transports Na^+ and K^+ ions in opposite directions (**antiport**) mediated by **Na^+-K^+ adenosine triphosphatase** (**ATPase**). Three Na^+ ions are pumped **out** of the cell, and two K^+ ions are pumped **into** the cell using the energy from the hydrolysis of a single ATP molecule by the ATPase.
   a. The primary function is to **maintain constant cell volume** by decreasing the intracellular ion concentration (and thus the osmotic pressure) and increasing the extracellular ion concentration, thus decreasing the flow of water into the cell.
   b. The Na^+-K^+ pump also plays a minor role in the maintenance of a **potential difference** across the cell membrane.
2. **Glucose transport** involves the **symport** movement of glucose across an epithelium (**transepithelial transport**). Transport is frequently along an electrochemical Na^+ gradient, via carrier proteins.
3. **ATP-binding cassette transporters** (**ABC transporters**) are transmembrane proteins that have two domains, the intracellularly facing **nucleotide-binding domain** (**ATP-binding domain**) and the **membrane-spanning domain** (**transmembrane domain**). In eukaryotes, ABC transporters use ATP to exocytose materials, such as toxins and drugs, from the cytoplasm into the extracellular space. ABC transporters may have additional functions, such as those of the placenta, which protect the developing fetus from **xenobiotics** (macromolecules such as antibiotics), not manufactured by cells of the mother.

CLINICAL CONSIDERATIONS

Multidrug-resistant proteins (**MDR proteins**) are **ABC transporters** present in certain cancer cells that are able to transport the cytotoxic drugs administered to treat the malignancy. In more than one-third of cancer patients, the malignant cells develop MDR proteins that interfere with the treatment modality being used.

C. Facilitated diffusion of ions can occur via ion channel proteins or ionophores.

1. **Selective ion channel proteins** permit only specific ions to traverse them. These channels may be ungated or gated.
   a. **K^+ leak channels** are the most common ion channels. These channels are ungated (i.e., they are always open) and leak K^+, the ions most responsible for establishing a potential difference across the plasmalemma.

b. Gated ion channels open only transiently in response to various stimuli. They include the following types:

(1) Voltage-gated channels open only when the potential difference across the membrane changes (e.g., voltage-gated Na^+ channels), which function in the generation of action potentials (see Chapter 8).

(2) Mechanically gated channels open in response to a mechanical stimulus (e.g., the tactile response of the hair cells in the inner ear).

(3) Ligand-gated channels open in response to the binding of a **signaling molecule** or **ion**. These channels include neurotransmitter-gated channels, nucleotide-gated channels, and G protein–gated K^+ channels of cardiac muscle cells.

CLINICAL CONSIDERATIONS

Ligand-gated ion channels are the likely targets of the anesthetic agents administered to block the spread of action potentials.

2. Ionophores are lipid-miscible molecules that form a complex with ions and insert into the phospholipid bilayer to transport those ions across the membrane. The two ways they perform this function are:

a. They completely surround the ion and pass through the phospholipid bilayer.

b. They insert into the cell membrane to form an ion channel with a hydrophilic lumen.

CLINICAL CONSIDERATIONS

Ionophores are frequently fed to cattle and poultry as antibiotic agents and growth-enhancing substances.

V. CELL-TO-CELL COMMUNICATION

A. Cells communicate with each other by sending *signaling molecules* to each other. The cell that synthesizes and releases the chemical is the **signaling cell** and the intended receiver cell is the **target cell**. In order to receive the signal, the target cell must have a **receptor molecule** to which the signaling molecule can bind. Signaling molecules can be **neurotransmitters** (released into synaptic clefts) and **hormones**. Hormones are of three types: **endocrine**, which use the bloodstream to be delivered to their target cells; **paracrine**, which is released into the extracellular space to a target cell in the near vicinity; and **autocrine**, which is released into the extracellular space to activate the signaling cell itself. The two major types of signaling molecules are:

1. **Lipid-soluble signaling molecules** or small **nonpolar molecules** (e.g., NO) that penetrate the cell membrane and bind to *receptors within the cytoplasm* or inside the **nucleus**, activating intracellular messengers. Examples include hormones that influence gene transcription.
2. **Hydrophilic signaling molecules** bind to and activate **cell surface receptors** (as do some lipid-soluble signaling molecules) and have diverse physiologic effects (see Chapter 11). Examples include neurotransmitters and numerous hormones (e.g., serotonin, thyroid-stimulating hormone, insulin).

B. Membrane receptors are primarily integral membrane glycoproteins. They are embedded in the phospholipid bilayer and have three domains, an **extracellular domain** that protrudes into the extracellular space and has binding sites for the signaling molecule, a **transmembrane domain** that passes through the phospholipid bilayer, and an **intracellular domain** that is located on the cytoplasmic aspect of the phospholipid bilayer and contacts either peripheral proteins or cellular organelles, thereby ***transducing*** the extracellular contact into an intracellular event.

CLINICAL CONSIDERATIONS

Venoms, such as those of some poisonous snakes, inactivate acetylcholine receptors of skeletal muscle sarcolemma at neuromuscular junctions.

Autoimmune diseases may lead to the production of antibodies that specifically **bind to and activate certain cell membrane receptors**. An example is **Graves disease** (hyperthyroidism).

1. **Membrane receptor function**
   a. They **control plasmalemma permeability** by regulating the conformation of ion channel proteins.
   b. They **regulate the entry of molecules** into the cell.
   c. They **bind extracellular matrix molecules** to the cytoskeleton via **integrins**.
   d. They **act as transducers** to translate extracellular events into an intracellular response via second messenger systems.

CLINICAL CONSIDERATIONS

Certain pathogens have evolved to behave as normal ligands, a process known as **ligand mimicry**. These pathogens bind to membrane receptors and are able to make their way into the cell. An example of such ligand mimicry is the polyomavirus SV40, which binds to tyrosine kinase Axl to enter the cell. Polyomavirus SV40 is a deoxyribonucleic acid (DNA) virus that was believed to cause cancer in humans, but those conclusions have been questioned, and its role as a human carcinogen is still uncertain.

2. **Membrane receptor types**
   a. **Channel-linked receptors** bind a signaling molecule that temporarily opens or closes the gate, permitting or inhibiting the movement of ions across the cell membrane. Examples include **nicotinic acetylcholine receptors** on the muscle cell sarcolemma at the myoneural junction.
   b. **Catalytic receptors** are single-pass transmembrane proteins.
      (1) Their extracellular moiety is a receptor, and their **cytoplasmic component** is a protein kinase.
      (2) Some catalytic receptors lack an extracytoplasmic moiety and, as a result, are continuously activated; such defective receptors are coded for by some **oncogenes**.

CLINICAL CONSIDERATIONS

Binding of insulin to the membrane-bound **insulin receptor** causes it to autophosphorylate and become endocytosed into the cytoplasm, where the complex becomes functional, inducing the cell to transport glucose from the extracellular fluid into the cytoplasm (mostly hepatocytes, adipose cells, and muscle cells).

   c. **G protein–linked receptors are** transmembrane proteins associated with an ion channel or with an enzyme that is bound to the cytoplasmic surface of the cell membrane.
      (1) These receptors interact with **heterotrimeric G protein** (guanosine triphosphate [GTP]-binding regulatory protein) after binding of a signaling molecule. The heterotrimeric G protein is composed of three subunits: **α and a β and γ complex**. The binding of the signaling molecule causes either:
         (a) The dissociation of the α-subunit from the β and γ complex where the α-subunit interacts with its target or
         (b) The three subunits do not dissociate, but either the α-subunit and/or the **β and γ complex** become activated and can interact with their targets.

      This interaction results in the activation of **intracellular second messengers**, the most common of which are cyclic adenosine monophosphate (**cAMP**), **Ca^{2+}**, and the **inositol phospholipid signaling pathway**.
      (2) Examples include the following:
         (a) **Heterotrimeric G proteins** (Table 1.2) are folded so that they make seven passes as they penetrate the cell membrane. These are stimulatory G protein (**G_s**; Fig. 1.6); inhibitory G protein (**G_i**); phospholipase C activator G protein (**G_q**); olfactory-specific G protein (**G_{olf}**); transducin (**G_t**); **G_o**, which acts to open K^+ channels and close Ca^{2+} channels; and **$G_{12/13}$**, which controls the formation of the actin component of the cytoskeleton and facilitates migration of the cell.
         (b) **Monomeric G proteins** (**low-molecular-weight G proteins**) are small single-chain proteins that also function in signal transduction.
            1. Various subtypes resemble Ras, Rho, Rab, and adenosine diphosphate (**ADP**) **ribosylation factor** (**ARF**) proteins.
            2. These proteins are involved in pathways that regulate cell proliferation and differentiation, protein synthesis, attachment of cells to the extracellular matrix, exocytosis, and vesicular traffic.

CLINICAL CONSIDERATIONS

Cholera toxin is an exotoxin produced by the bacterium *Vibrio cholerae* that alters $\mathbf{G_s}$ protein so that it is unable to hydrolyze its GTP molecule. As a result, cAMP levels increase in the surface-absorptive cells of the intestine, leading to excessive loss of electrolytes and water and severe diarrhea.

Pertussis toxin, the product of the bacterium that causes whooping cough, inserts ADP-ribose into the α-subunits of trimeric G proteins, causing the accumulation of the inactive form of G proteins, resulting in irritation of the mucosa of the bronchial passages.

Defective $\mathbf{G_s}$ proteins may lead to mental retardation, diminished growth and sexual development, and decreased responses to certain hormones.

table **1.2** Functions and Examples of Heterotrimeric G Proteins

Type	Function	Result	Examples
G_s	Activates adenylate cyclase, leading to formation of cAMP	Activation of protein kinases	Binding of epinephrine to β-adrenergic receptors increases cAMP levels in cytosol
G_i	Inhibits adenylate cyclase, preventing formation of cAMP	Protein kinases remain inactive	Binding of epinephrine to α_2-adrenergic receptors decreases cAMP levels in cytosol
G_q	Activates phospholipase C, leading to formation of inositol triphosphate and diacylglycerol	Influx of Ca^{2+} into cytosol and activation of protein kinase C	Binding of antigen to membrane-bound IgE causes the release of histamine by mast cells
G_o	Opens K^+ channels and closes Ca^{2+} channels	Inhibits adenylate cyclase Influx of K^+ and limits Ca^{2+} movement	Inducing contraction of smooth muscle
G_{olf}	Activates adenylate cyclase in olfactory neurons	Opens cAMP-gated Na^+ channels	Binding of odorant to G protein–linked receptors initiates generation of nerve impulse
G_t	Activates cGMP phosphodiesterase in rod cell membranes, leading to hydrolysis of cGMP	Hyperpolarization of rod cell membrane	Photon activation of rhodopsin causes rod cells to fire
$G_{12/13}$	Activates Rho family of guanosine triphosphatases	Regulates cytoskeleton assembly by controlling actin formation	Facilitating cellular migration

cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; IgE immunoglobulin E.

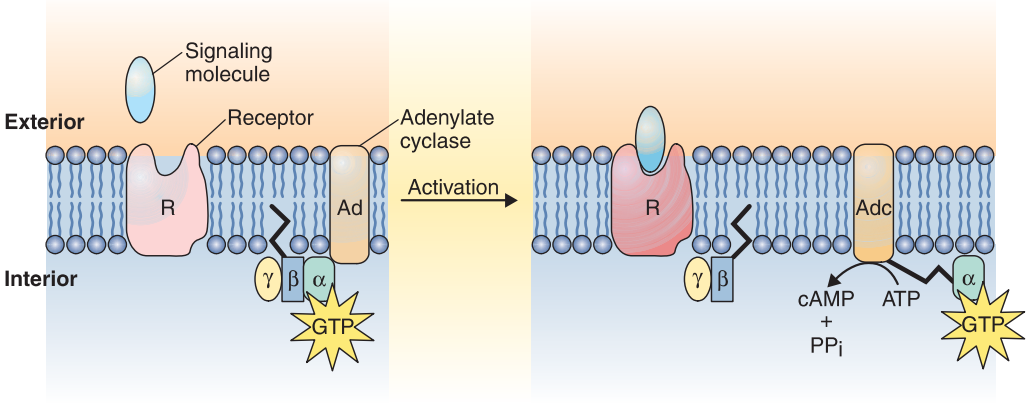


FIGURE 1.6. Functioning of G_s protein–linked receptors. The signaling molecule binds to the receptor, which causes the α-subunit of the G_s protein to bind to guanosine triphosphate (GTP) and dissociate from the β- and γ-subunits. Activation of adenylate cyclase by the GTP–α-subunit complex stimulates synthesis of cyclic adenosine monophosphate (cAMP), one of the most common intracellular messengers. ATP, adenosine triphosphate.

VI. PLASMALEMMA—CYTOSKELETON ASSOCIATION

The plasmalemma and cytoskeleton associate through **integrins**. The extracellular domain of integrins binds to extracellular matrix components, and the intracellular domain binds to cytoskeletal components. Integrins stabilize the plasmalemma and determine and maintain cell shape.

A. Red blood cells (Fig. 1.7A) have integrins, called *band 3 proteins*, which are located in the plasmalemma. The cytoskeleton of a red blood cell consists mainly of spectrin, actin, band 4.1 protein, and ankyrin.

1. **Spectrin** is a long, flexible protein (about 110 nm long), composed of an **α-chain** and a **β-chain**, that forms **tetramers** and provides a scaffold for structural reinforcement.
2. **Actin** attaches to binding sites on the spectrin tetramers and holds them together, thus aiding in the formation of a hexagonal spectrin latticework.
3. **Band 4.1 protein** binds to and stabilizes spectrin–actin complexes.
4. **Ankyrin** is linked to both band 3 proteins and spectrin tetramers, thus attaching the spectrin–actin complex to transmembrane proteins.

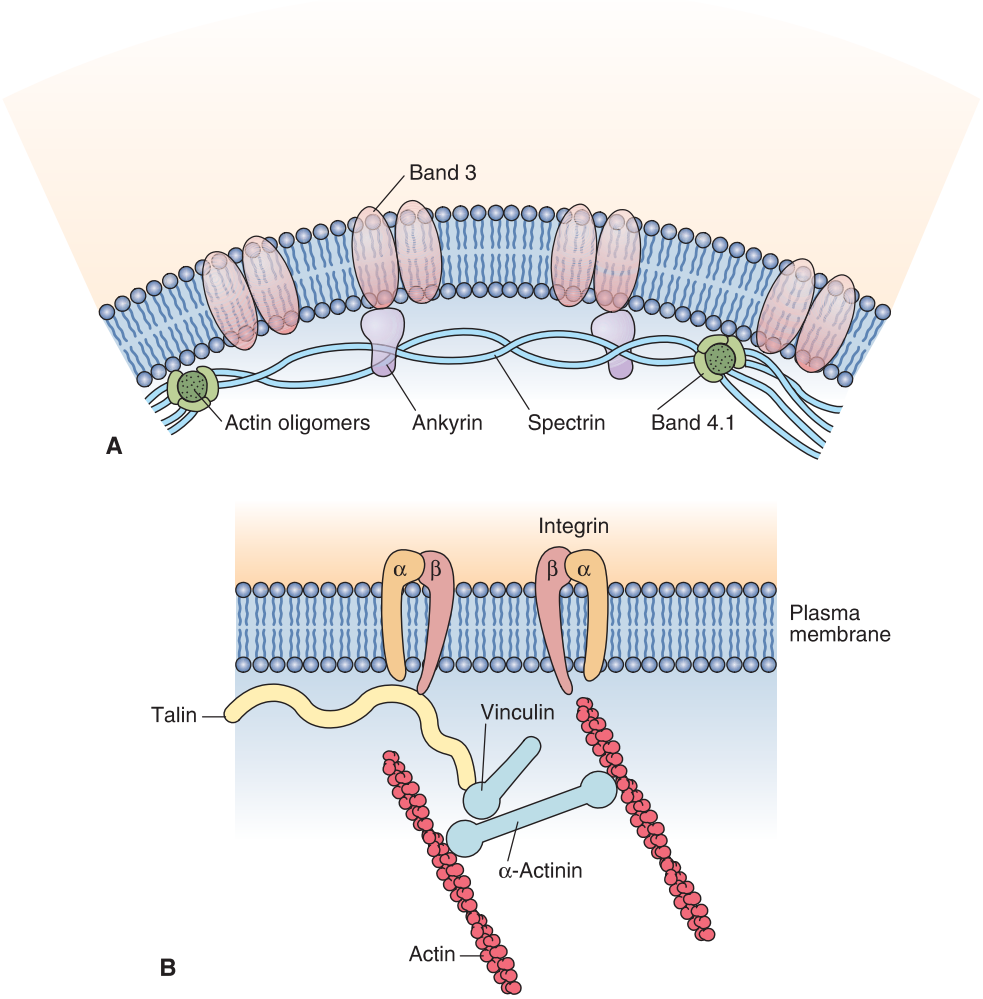


FIGURE 1.7. Plasmalemma–cytoskeleton association in red blood cells **(A)** and nonerythroid cells **(B)**. (Adapted with permission from Widnell CC, Pfenninger KH. *Essential Cell Biology*. Baltimore, MD: Williams & Wilkins; 1990:82.)

B. The cytoskeleton of nonerythroid cells (Fig. 1.7B) consists of the following major components:

1. **Actin** (and perhaps **fodrin**), which serves as a nonerythroid spectrin.
2. **α-Actinin**, which cross-links actin filaments to form a meshwork.
3. **Vinculin**, which binds to α-actinin and to another protein, called **talin**, which, in turn, attaches to the integrin in the cell membrane.

CLINICAL CONSIDERATIONS

Hereditary spherocytosis results from mutations in the genes coding for the membrane proteins **spectrin**, **ankyrin**, **band 3 protein**, or **protein 4.2** that have a decreased ability to bind to their various counterparts. The disease is present mostly in individuals whose ancestors were from northern Europe and is characterized by splenomegaly, anemia, and jaundice because of fragile, spherical red blood cells, referred to as **spherocytes**, whose destruction in the spleen leads to these conditions.

During high-speed car accidents and often in shaken baby syndrome, the sudden accelerating and decelerating forces applied to the brain cause shearing damage to axons, especially at the interface between white matter and gray matter. The stretching of the axons results in **diffuse axonal injury**, a widespread lesion that causes a persistent coma from which only 10% of affected individuals regain consciousness. Examination of the affected tissue displays irreparable cleavage of **spectrin**, with an ensuing destruction of the neuronal cytoskeleton, leading to loss of cell membrane integrity and eventual cell death.

VII. CYTOPLASMIC STRUCTURAL COMPONENTS

A. Organelles are metabolically active units of the cell.

1. **Ribosomes**
   - **a. Structure.** Ribosomes are nonmembranous organelles (12 nm wide and 25 nm long) that consist of a **small** and a **large subunit**. The two subunits are composed of several types of ribosomal ribonucleic acids (rRNAs) and numerous proteins (Table 1.3; Fig. 1.8).
   - **b.** Ribosomes constitute a single interchangeable population whether they are (1) located free in the cytosol; (2) bound to membranes of the rough endoplasmic reticulum (RER); and (3) attached to the cytoplasmic surface of the outer nuclear membrane.
   - **c.** A **polyribosome** (**polysome**) is a cluster of ribosomes along a single strand of messenger ribonucleic acid (mRNA) where every ribosome is concurrently engaged in protein synthesis.
   - **d. Function.** Ribosomes are organelles on which **mRNA is translated into protein**. Proteins destined for transport (secretory, membrane, and lysosomal) are synthesized on polyribosomes bound to the RER, whereas proteins destined to remain in the cytosol are synthesized on polyribosomes in the cytosol. Cytosolic protein synthesis occurs in the following manner (synthesis of proteins destined to be transported is discussed in Section VIII B Organelle Interactions).
     - **(1)** The **small ribosomal subunit** binds both mRNA and activated transfer ribonucleic acids (tRNAs); the **codons** of the mRNA then **base-pair** with the corresponding **anticodons** of the tRNAs.
     - **(2)** Next, an initiator tRNA recognizes the **start codon** (**AUG**) on the mRNA.
     - **(3)** The **large ribosomal subunit** then binds to the complex. The enzyme **peptidyl transferase** located in the large subunit catalyzes peptide bond formation, resulting in addition of amino acids to the growing polypeptide chain.

table 1.3 Ribosome Composition

Subunit	rRNA Types	Number of Proteins
Large (60S)	5S 5.8S 28S	49
Small (40S)	18S	33

rRNA, ribosomal ribonucleic acid.

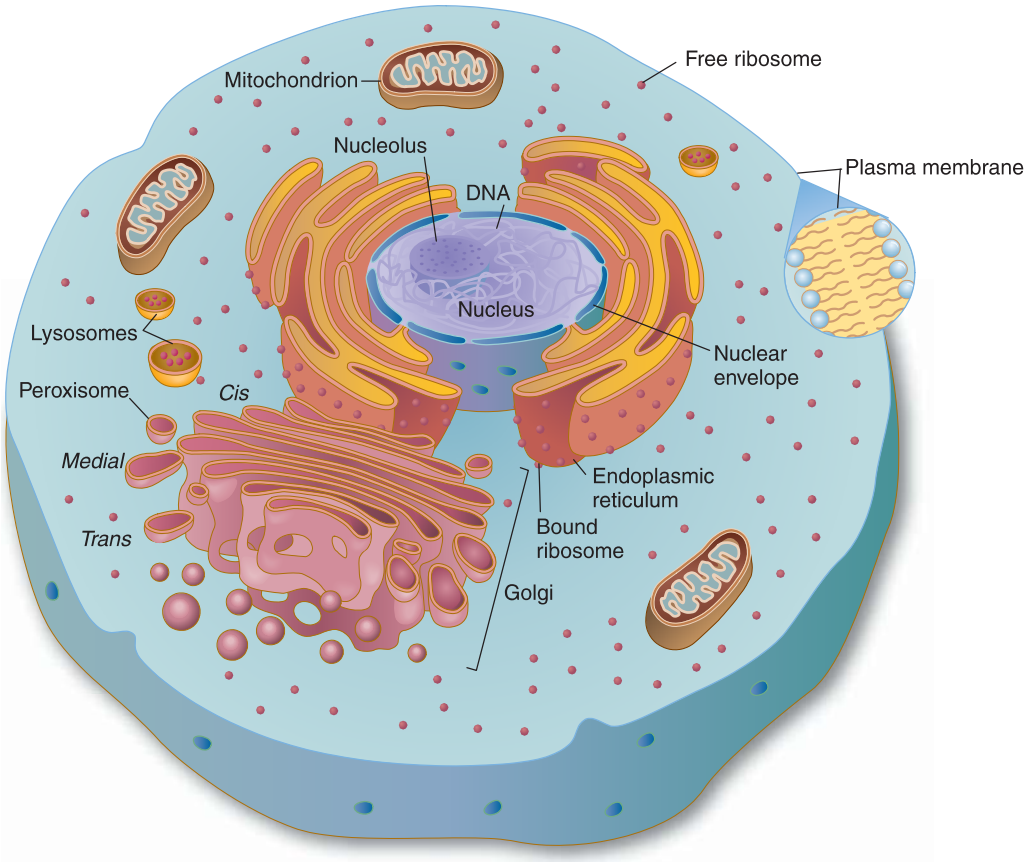


FIGURE 1.8. A eukaryotic cell and its major organelles and inclusions. DNA, deoxyribonucleic acid. (Reprinted with permission from Chandar N, Viselli S. *LIR Cell and Molecular Biology*. 2nd ed. North American ed. Baltimore, MD: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2018.)

(4) A **chain-terminating codon** (**UAA**, **UAG**, or **UGA**) causes release of the polypeptide from the ribosome, and the ribosomal subunits dissociate from the mRNA.

2. **RER** (Figs. 1.8 and 1.9)
   - **a. Structure.** RER, as apparent in TEM, is a system of membrane-bounded sacs, or narrow tubules whose outer surface is studded with **ribosomes**, whose large subunit binds to proteins, called **ribophorins**, located in the outer RER membrane. The lumen of the RER is called the **cisterna**. The outer nuclear membrane is **continuous** with the RER; therefore, its lumen, the **perinuclear cistern**, is confluent with the cisternae of the RER.
   - **b.** RER is abundant in cells synthesizing **secretory proteins**; in such cells, the RER is organized into many parallel arrays of flat stacks.
   - **c.** The RER sac closest to the Golgi apparatus gives rise to buds free of ribosomes that form vesicles known as **transfer vesicles**. This sac is known as a **transitional element** and represents the region of exit from the RER.
   - **d. Function.** The RER is where **proteins** that are to be packaged are synthesized, including secretory, cell membrane, and lysosomal proteins. The RER **monitors** the assembly, retention, and even degradation of certain proteins. Proteins that are to be retained in the RER cisternae are marked by the presence of a small peptide at their C terminus, known as the **KDEL sequence**, composed of lysine, asparagine, glutamine, and leucine. Proteins that do not sport the KDEL sequence at the C terminus are transported out of the cisternae of the RER.
3. **Smooth endoplasmic reticulum** (**SER**)
   - **a. Structure.** SER is an irregular network of membrane-bounded channels that lack ribosomes on its surface, which makes it appear smooth.

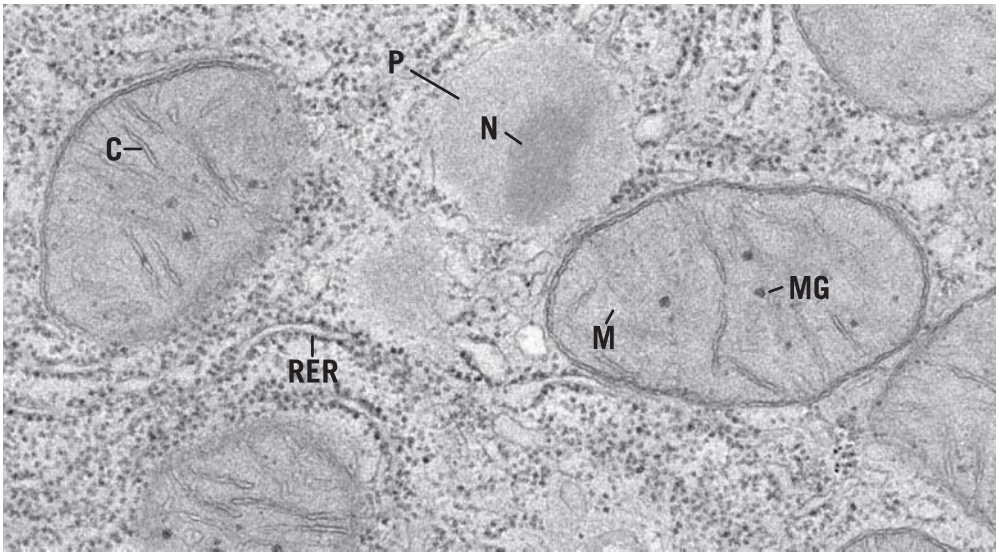


FIGURE 1.9. An electron micrograph showing rough endoplasmic reticulum (RER); portions of several mitochondria and their cristae (C), matrix (M), and matrix granules (MG); and a peroxisome (P) with a nucleoid (N).

b. It usually appears as branching, anastomosing **tubules**, or **vesicles**, whose membranes do **not** contain ribophorins.

c. SER is less common than RER but is prominent in cells synthesizing steroids, triglycerides, and cholesterol.

d. Function. SER has different functions in different cell types.

(1) Steroid hormone synthesis occurs in SER-rich cells such as the Leydig cells of the testis, which make testosterone.

(2) Fatty acid and phospholipid synthesizing cells are rich in SER.

(3) Drug detoxification occurs in hepatocytes following proliferation of the SER in response to the drug phenobarbital; the oxidases that metabolize this drug are located in the SER.

(4) Muscle contraction and relaxation involve the release and recapture of Ca^{2+} by the SER in skeletal muscle cells, called the sarcoplasmic reticulum.

4. Peripheral endoplasmic reticulum. Recent studies have reported that in a number of cell types, the ER that is located in the periphery of the cell may appear to be composed of flattened sheets but is, in fact, composed of thin tubules that frequently are in motion.

a. As they diverge from each other, they are seen as tubular structures that may rapidly congregate to give the appearance of flat sheets. Interestingly, most of these tubules sport ribosomes.

b. In order to maintain their morphology, whether flat sheets or narrow tubules, and to form junctions with each other, they require the presence of specific families of **ER-shaping proteins** that act as scaffoldings and buttresses.

(1) Members of the **reticulon family** of proteins maintain the stability of the curvatures of the ER.

(2) Members of the **atlastin** family of proteins support the formation of junctions with other ER tubules.

(3) Members of the **kinectin** family of proteins support the formation of flattened sheets of the RER and assist in maintaining a constant luminal size.

CLINICAL CONSIDERATIONS

Mutations in the ER-shaping proteins may have serious clinical consequences. Some of these altered proteins are responsible for a condition known as **hereditary spastic paraplegia** that affects some of the neurons responsible for limb movement. The absence of normal scaffolding protein prevents the ER tubules from forming three-way junctions with each other, thereby interfering with the ability of the ER to form lipids, resulting in abnormal lipid metabolism and myelin formation. The reduction in myelin in the axons of the primary motor neurons results in spastic limb movements.

5. **Mitochondria** (see Figs. 1.8 and 1.9)
   a. **Structure. Mitochondria** are rod-shaped organelles (at least 0.5 μm wide and as much as 7 μm in length) that possess an **outer membrane** that surrounds the organelle and an **inner membrane**, rich in **cardiolipin**, which invaginates to form **cristae**. Mitochondria are subdivided into an **intermembrane compartment** between the two membranes and an inner, dense fluid (**matrix**) containing **matrix compartment**. Granules within the matrix bind the divalent cations Mg^{2+} and Ca^{2+}.
   b. **Enzymes and genetic apparatus.** Mitochondria contain:
      (1) All of the enzymes of the **Krebs** (**tricarboxylic acid**) **cycle** are in the matrix, except for **succinate dehydrogenase**, which is embedded in the inner mitochondrial membrane.
      (2) **Elementary particles** (visible on negatively stained cristae) represent **ATP synthase**, a special enzyme embedded in the inner mitochondrial membrane. It consists of a head portion and a transmembrane H^+ carrier and is involved in **coupling oxidation** to **phosphorylation** of ADP to form ATP (Fig. 1.10).
      (3) The **genetic apparatus** in the matrix is composed of circular DNA with a limited number of genes, mRNA, tRNA, and rRNA. The majority of mitochondrial proteins are encoded by the DNA located in the nucleus.
      (4) Proteins formed in the cytosol that are destined for incorporation into mitochondria must have positively charged terminal amino acids and must be accompanied by **cytosolic heat shock protein 70**. These two signals are recognized by a carrier molecule known as **translocase of the outer mitochondrial membrane complexes** embedded in the outer mitochondrial membrane. The recognition permits the translocation of the protein into the intermembrane compartment from which the protein enters the matrix compartment via the **inner mitochondrial membrane complexes**. Once in the matrix, mitochondrial heat shock protein 70 cleaves the terminal positive amino acids.
   c. **Origin and proliferation**
      (1) Mitochondria may have originated as **intracellular symbionts** (intracellular parasites).
      (2) Mitochondria proliferate by division (fission) of preexisting mitochondria and typically have a 10-day life span. Proteins needed to sustain mitochondria are imported into them from the cytosol.

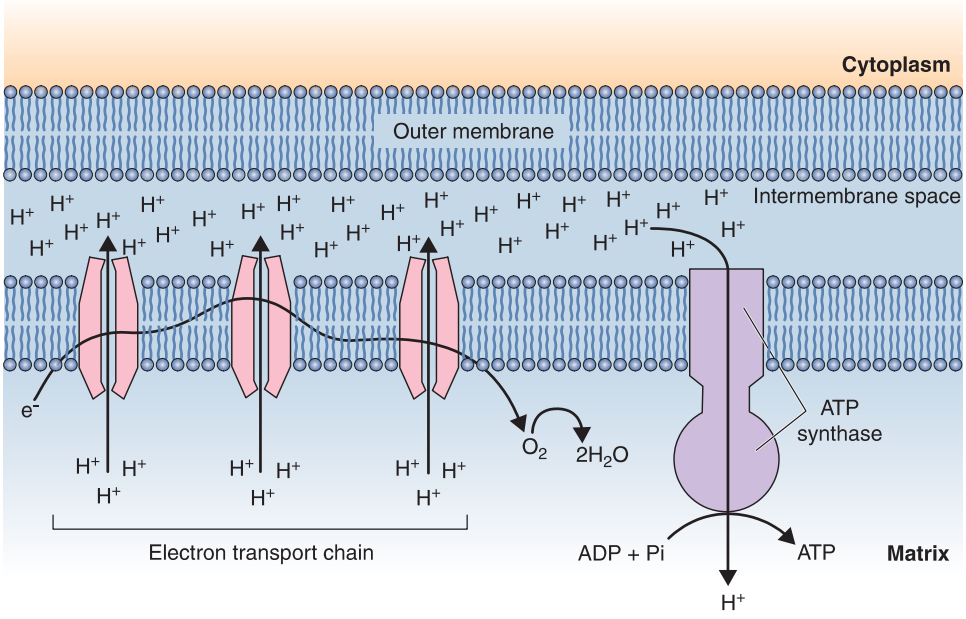


FIGURE 1.10. Chemiosmotic coupling mechanism for generating adenosine triphosphate (ATP) in mitochondria. As electrons move (sequentially) along the enzyme complexes of the electron transport chain, H^+ ions (protons) are pumped from the matrix compartment across the inner mitochondrial membrane into the intermembrane compartment generating a proton gradient. This electrochemical proton gradient drives the production of ATP as protons pass down their electrochemical gradient through ATP synthase and reenter the matrix. As H^+ passes through ATP synthase, this enzyme uses the energy of the proton flow to drive the production of ATP from adenosine diphosphate (ADP) and Pi.

d. **Mitochondrial ATP synthesis occurs in two ways:**
   (1) ATP is synthesized via the Krebs cycle, which traps chemical energy and produces ATP by **oxidation** of fatty acids, amino acids, and glucose.
   (2) ATP is also synthesized via a **chemiosmotic coupling mechanism** involving enzyme complexes of the **electron transport chain** (composed of **nicotinamide adenine dinucleotide dehydrogenase complex**, **cytochrome b_1-c complex**, and **cytochrome oxidase complex** through which **energy-rich protons** enter the intermembrane compartment) and **ATP synthase** present in elementary particles of cristae (see Fig. 1.10). The energy-rich protons leave the intermembrane compartment through the ATP synthase to reenter the matrix compartment where they yield their energy to **ADP + Pi** (where Pi is **inorganic phosphate** derived from the cytosol) to form **ATP**.
   (3) ADP is transported into the organelle via **ADP/ATP exchange proteins** located in both the outer and inner mitochondrial membranes. As their name implies, these exchange proteins allow ADP to enter and ATP to exit the mitochondrion.

e. **Condensed mitochondria** result from a **conformational change** in the orthodox form (typical morphology) because of an uncoupling of oxidation from phosphorylation. The size of the inner compartment is decreased, the matrix density is increased, and the intermembrane compartment is enlarged.
   (1) Condensed mitochondria are present in **brown fat cells**, which produce **heat**, rather than ATP because they have a special transport protein in their inner membrane, **thermogenins**, that **uncouples** respiration from ATP synthesis (see Chapter 4).

CLINICAL CONSIDERATIONS

Swollen mitochondria have been observed in response to calcium, phosphate, and thyroxin, which induce an increase in water uptake and an uncoupling of phosphorylation; ATP reverses the swelling.

Some mitochondrial diseases, such as **Leigh disease**, are due to mutations either in the mitochondrial DNA itself or to mutations in the nuclear DNA that codes for mitochondrial proteins. Although Leigh disease is rare, it is lethal within the first year or so of life and rarely does the affected individual reach age 10 or more. Most of the body's tissues that have a high energy requirement (skeletal and cardiac muscles; neurons) decline because the cells' mitochondria are unable to provide enough energy to maintain them in a healthy condition. Therefore, the muscular system, heart, and many neurons progressively deteriorate. It appears that most mitochondria of an affected individual have malformations in one or more of the enzymes responsible for oxidative phosphorylation. Recently it has become possible to have children born of "three parents," if the birth mother already had a child born with Leigh disease. The procedure involves transferring the nucleus of the birth mother's egg to a donor's egg with its original nucleus removed, which is then fertilized by the father's spermatozoa. The fertilized egg is implanted in the birth mother. Because all of the mitochondria of the fetus is derived from the egg, the normal mitochondria of the donor are able to replace the defective mitochondria of the birth mother. Because the existence of such "three-parent" babies is very recent, no long-term complications have yet been observed or documented.

6. **Golgi apparatus** (**complex**) (Figs. 1.11 and 1.12; also see Fig. 1.8)
   a. **Structure.** The Golgi apparatus consists of several membrane-bounded **cisternae** (**saccules**) arranged in a **stack** and positioned and held in place by microtubules. Cisternae are disk shaped (each resembling a pita bread) and slightly curved, with flat centers and dilated rims, but their size and shapes vary. The morphology of these units is due to the presence of Golgi membrane–associated proteins; additionally, **F-actins** connect the cisternae to each other. A distinct **polarity** exists across the Golgi stack, with many vesicles present near the nucleus (the entry side into the Golgi apparatus) and larger secretory granules (vacuoles) away from the nucleus (the exit side of the Golgi apparatus).
   b. **Regions**
      (1) The ***cis* face** of the Golgi apparatus typically lies deep in the cell toward the nucleus next to the **transitional element** of the RER. Its outermost cisterna is associated with a network

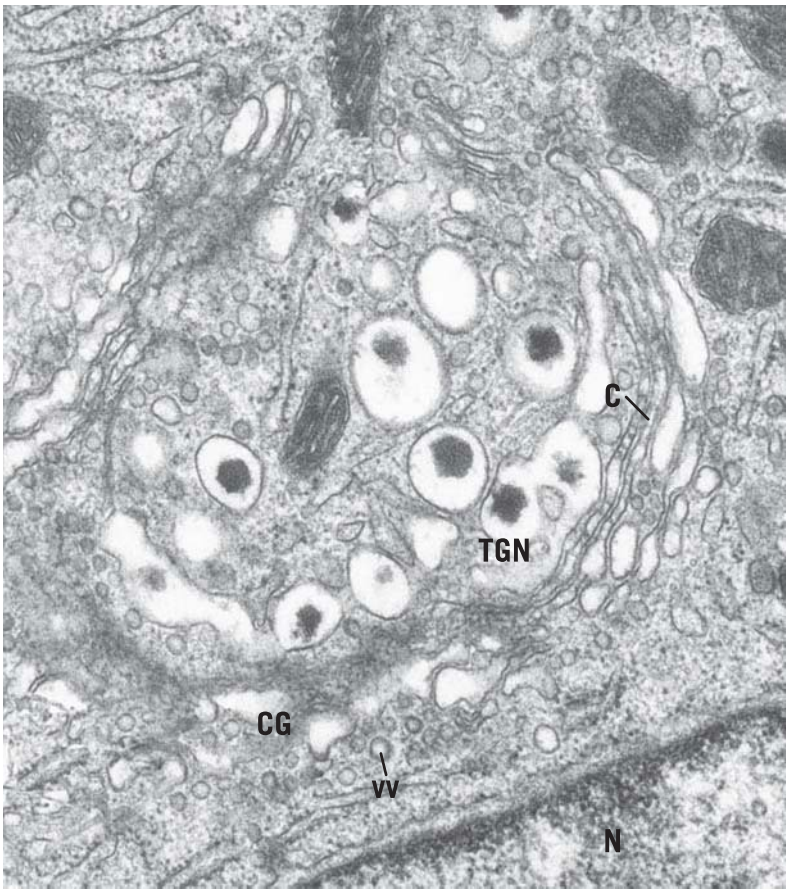


FIGURE 1.11. Electron micrograph of a Golgi apparatus showing a *trans*-Golgi network (TGN) with vacuoles and forming secretory granules, Golgi cisternae (C), and a vesicular–tubular cluster delivering proteins to the *cis*-Golgi (CG) via tiny vesicles (vv). A portion of a nucleus (N) is also evident.

of interconnected tubes and vesicles, called **vesicular–tubular clusters** (**VTC**; previously known as ERGIC), which receives **transfer vesicles** from the transitional element of the RER (see Figs. 1.11 and 1.12).

(2) The **medial compartment** of the Golgi apparatus is composed of several cisternae located between the *cis* and *trans* faces.

(3) The ***trans* face** of the Golgi apparatus lies at the side of the stack facing the cell membrane and is associated with vacuoles and secretory granules.

(4) The ***trans*-Golgi network** (**TGN**) lies apart from the last cisterna at the *trans* face and is separated from the Golgi stack. It sorts proteins for their final destinations.

c. Functions. The Golgi apparatus synthesizes carbohydrates, processes membrane-packaged proteins synthesized in the RER, and also recycles and redistributes membranes.

7. Coated vesicles are characterized by a visible cytoplasmic surface coat.

a. Clathrin-coated vesicles (Fig. 1.13)

(1) Structure. These vesicles are coated with **clathrin**, a protein composed of three large and three small polypeptide chains that form a **triskelion** (three-legged structure). Four classes of adaptins, two large ones named α-adaptin and β-adaptin, a medium-sized one known as μ-adaptin, and the smallest one, σ-adaptin, form a part of the clathrin coat. A μ-adaptin, a σ-adaptin, and two of the large adaptins combine to form an **adaptin complex** (also known as an **adaptor**) and assist in capturing cargo receptors containing specific molecules, and they help to establish the vesicle curvature. A GTP-binding protein called **dynamin** forms a ring around the neck of a budding vesicle or pit and aids in pinching it off the parent membrane to form a free clathrin-coated vesicle (see Fig. 1.13).

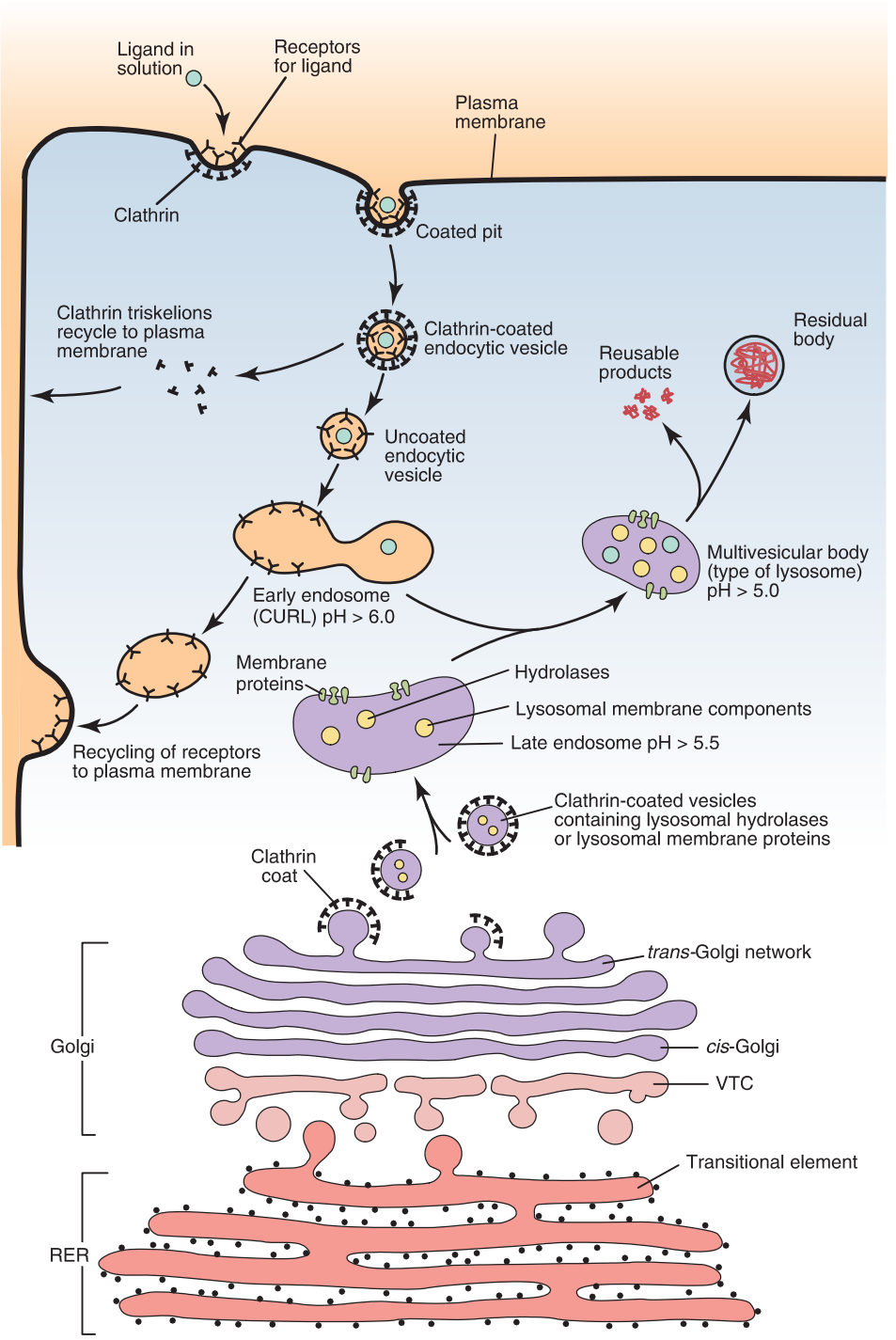


FIGURE 1.12. Receptor-mediated endocytosis of a ligand (e.g., low-density lipoproteins) and the lysosomal degradative pathway. Clathrin triskelions quickly recycle back to the cell membrane. The receptors and ligands then uncouple in the early endosome (compartment for uncoupling of receptors and ligands [CURL]), which is followed by recycling of receptors back to the cell membrane. The late endosome is the primary intermediate in the formation of lysosomes (e.g., multivesicular bodies). Material that is phagocytosed or organelles that undergo autophagy do not use the early endosomal pathway. RER, rough endoplasmic reticulum; VTC, vesicular–tubular cluster.

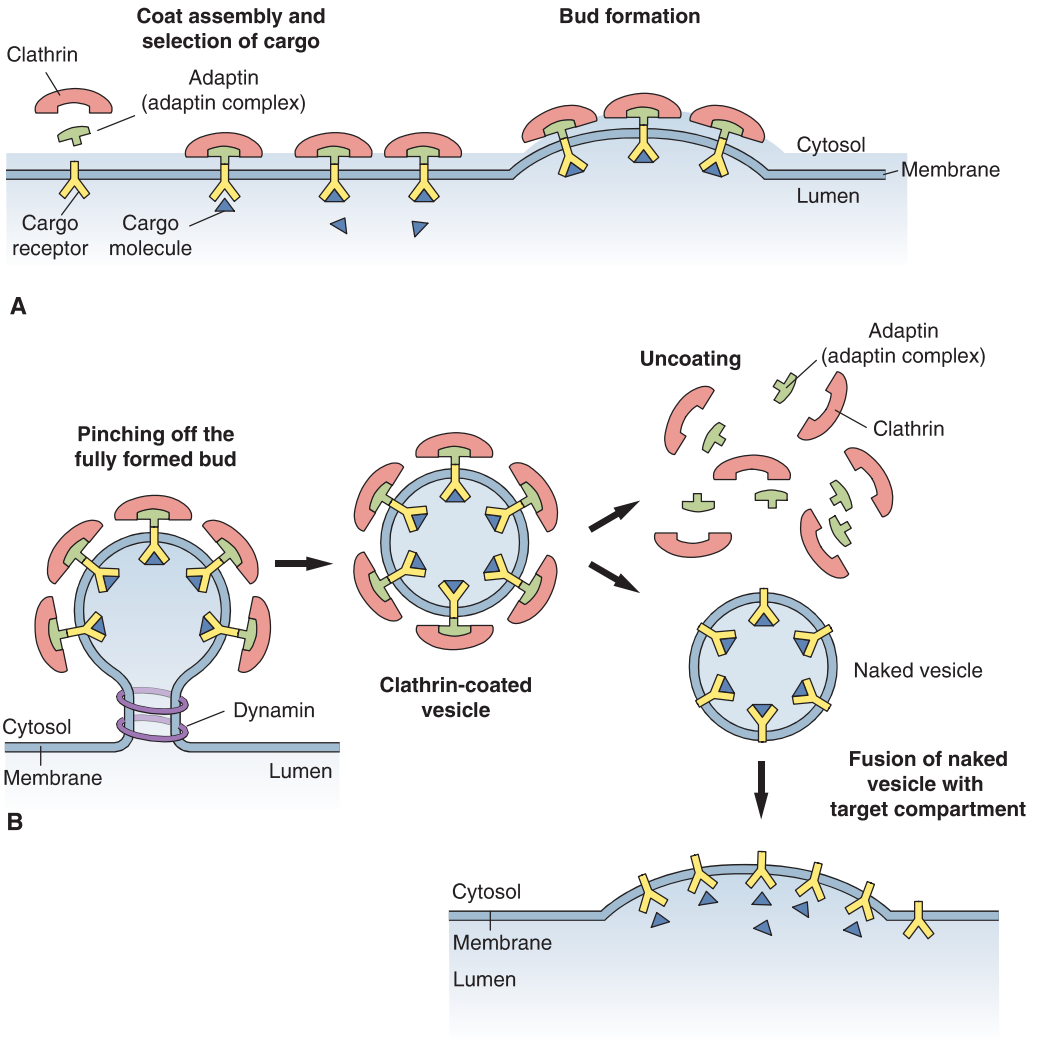


FIGURE 1.13. Formation and disassembly of a clathrin-coated vesicle involved in the transport of selected cargo molecules. **A.** Cargo receptors in the membrane of a donor organelle recognize transport signals on cargo molecules and select specific molecules. Adaptin (adaptin complex) coat proteins recognize and bind the specific cargo receptors that have captured a selected set of cargo molecules, ensuring that only they will be incorporated into the lumen of the new clathrin-coated vesicle. Adaptin also recruits clathrin and binds it to the outer surface of the forming bud. **B.** As the budding vesicle becomes fully formed, dynamin proteins assemble around its neck and constrict it to pinch off the vesicle. The clathrin and adaptin are quickly removed, and the uncoated (naked) vesicle then fuses with the membrane of its target organelle and releases the cargo molecules into its lumen. (Copyright from Alberts B, Johnson A, Lewis J, et al. *Molecular Biology of the Cell*. 4th ed. New York, NY: Garland Science; 2002. Adapted with permission from Garland Science/Taylor & Francis LLC.)

(2) Function

(a) Clathrin-coated vesicles are formed during **receptor-mediated uptake** (**endocytosis**) of specific molecules by the cell. The vesicles quickly lose their coats after endocytosis, and clathrin and adaptin complexes return to the cell membrane (see Fig. 1.12).

(b) Clathrin-coated vesicles also function in the **signal-directed** (**regulated**) **transport** of proteins from the TGN either to the secretory granule pathway or to the late endosome–lysosome pathway. After the clathrin-coated vesicle loses its coat, the naked vesicle fuses with a donor membrane compartment, and the clathrin and adaptin molecules are reused within the cell (see Fig. 1.13).

b. Coatomer-coated vesicles

(1) Structure. These vesicles, instead of clathrin, have coats consisting of **coatomer**, a large protein complex formed by individual **co**at **p**rotein subunits called **COPs**. ARF (ADP-ribosylation

factor), which binds GTP, is required for coatomer assembly. ARF becomes activated, and not only recruits coatomer subunits but also assists in selecting cargo molecules. The two types of COPs are **COP-I** and **COP-II**.

(2) **Function**

(a) **Coatomer-coated vesicles** mediate the continuous **constitutive protein transport** (default pathway; bulk flow) within the cell. Specific GTP-binding proteins are present at each step of vesicle budding and fusion, and proteins called **SNAREs** (**soluble NSF attachment proteins** [***SNAP***] ***re*ceptors**) ensure that the vesicle docks and fuses only with its correct target membrane. **Coated vesicle SNAREs** (v-SNAREs) recognize and bind to complementary **target SNAREs** (t-SNAREs) to deliver not only cargo molecules but also membrane to the target compartment (Fig. 1.14). Once the t-SNAREs and

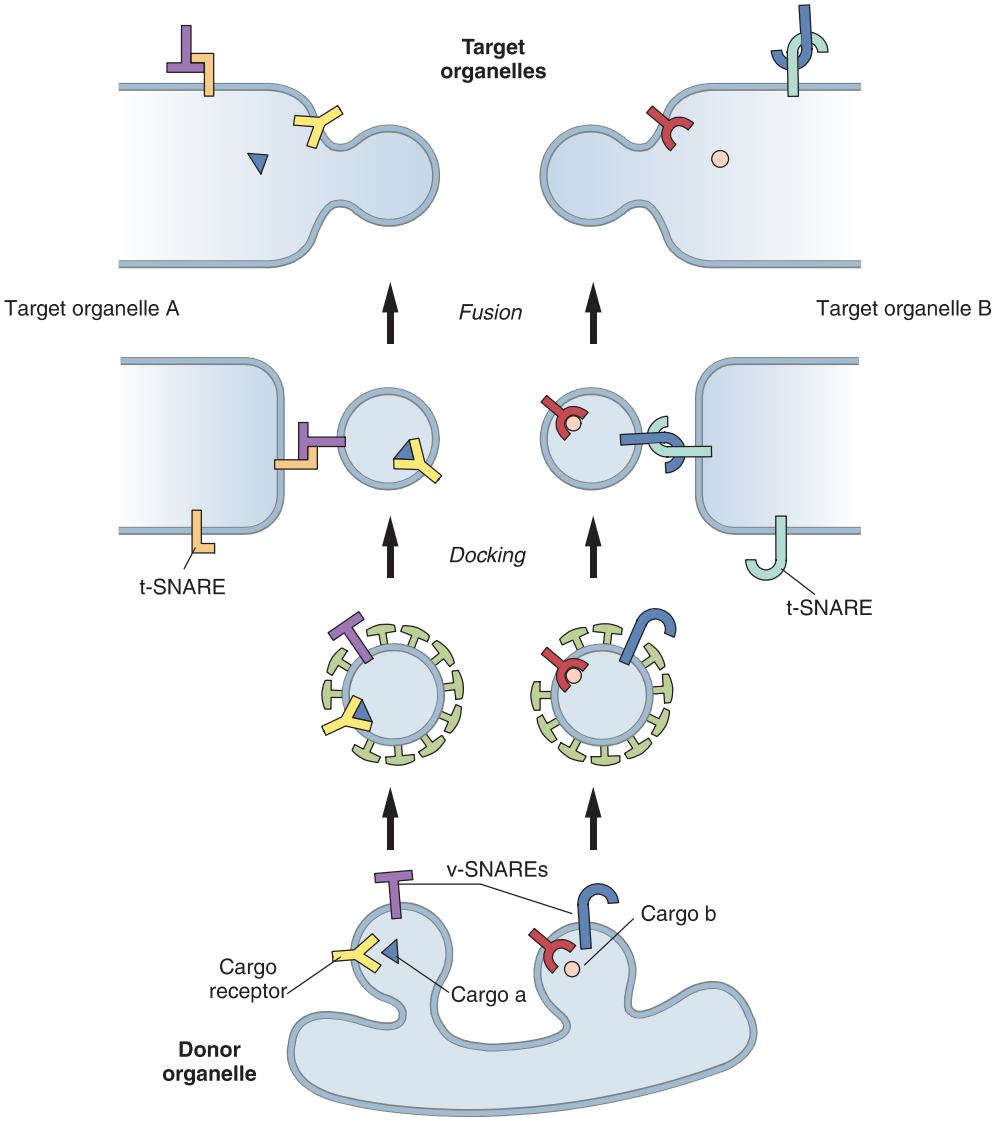


FIGURE 1.14. Coated vesicles are moved along cytoskeletal elements to their destination by motor molecules, but once there, they must recognize and fuse with only the correct target organelle membrane. This is achieved by proteins on the surface of the vesicle, called vesicle SNAREs (v-SNAREs), that recognize and bind to complementary target SNAREs (t-SNAREs) on the membrane of the correct target organelle. First docking of the vesicle and then fusion occur as the vesicle not only contributes its contents (cargo) but also adds its membrane to that of the organelle. (Copyright from Alberts B, Johnson A, Lewis J, et al. *Molecular Biology of the Cell*. 4th ed. New York, NY: Garland Science; 2002. Adapted with permission from Garland Science/Taylor & Francis LLC.)

v-SNAREs recognize each other they enlist the help of two additional cytosolic proteins, ***N*-ethylmaleimide-sensitive-fusion** (**SNF**) and **SNAP**. The four proteins, SNAP, SNF, t-SNARE, and v-SNARE, together accomplish the process of fusion between the specific target membrane and the cargo-carrying vesicle.

(b) Coatomer-coated vesicles transport proteins from the RER to the VTC, then to the Golgi apparatus, and from one Golgi cisterna to another.

1. COP-II transports molecules *forward* from the RER to the VTC to the *cis*-Golgi (**anterograde transport**).
2. COP-I facilitates **retrograde transport** (from the VTC or any Golgi cisternal compartment or from the TGN) to the RER. Whether or not COP-I facilitates anterograde transport is still questionable, but recent findings suggest that they might move forward between Golgi regions (*cis*-Golgi to medial Golgi to *trans*-Golgi) and the TGN.

CLINICAL CONSIDERATIONS

The interaction of v-SNARES with t-SNARES is essential for neurotransmitter release, via exocytosis, at chemical synapses. At the presynaptic nerve terminal, one of the t-SNARES is SNAP-25, a fusion protein. **Botox** (botulinum neurotoxin A) cleaves SNAP-25 and prevents the synaptic vesicles from anchoring and releasing their neurotransmitter, thus preventing neuromuscular transmission and contraction. This leads to a flaccid paralysis of the postsynaptic muscle.

c. Other vesicles

(1) Caveolin-coated vesicles. Caveolae are **caveolin-coated** invaginations of the cell membrane in endothelial and smooth muscle cells.

(2) Retromer-coated vesicles are present only in the retrieval of cargo from **endosomes** and returned to the **TGN**. Retromers are composed of four subunits that can assemble only if the correct cytoplasmic component of the cargo receptor protein is available for binding to one of the retromer subunits, and if the membrane possesses a particular **inositol phospholipid**, known as **phosphoinositide** (**PIP**), that is recognized by another one of the retromer subunits. The presence of the various types of PIPs and their ability to be altered to different forms act as signaling molecules for the various COPs (Table 1.4).

(3) Rab proteins (**Rab-GTPs**) are another large family of monomeric GTPases that are also involved in the molecular mechanism of membrane transport. More than 70 types of Rab proteins exist (some are listed in Table 1.5), and they are attached to vesicle and/or target membranes via prenyl groups. The target membranes also possess **Rab effector proteins** (**tethering proteins**) that recognize specific Rab-GTPs, bind to them, and in this fashion direct the vesicle to the target membrane, where v-SNARE is able to contact t-SNARE, thus facilitating membrane fusion. If the Rab-GTP is not recognized, then the vesicle cannot dock, assuring that the particular vesicle can fuse only with its intended target membrane. Subsequent to the fusion of the vesicle with its target membrane the Rab protein is recycled to its membrane of origin.

table 1.4 Membrane Locations of PIPs

PIP	Location
PI(3)P	Early endosomes; phagosome membrane
PI(4)P	TGN; lateral cell membrane
PI(4,5)P_2	Golgi; lateral cell membrane; apical cell membrane
PI(3,5)P_2	Late endosomes
PI(3,4,5)P_3	Apical cell membrane

PI(3)P indicates that there is only one phosphate group, and it is located at the 3′ position; PI(3,5)P_2 indicates that there are two phosphate groups, where one is at the 3′ and the other is at the 5′ position; PI(3,4,5)P_3 indicates that there are three phosphate groups, one at the 3′, one at the 4′, and the third one at the 5′ position.
PIP, phosphoinositide; TGN, *trans*-Golgi network.

table 1.5 Locations of Selected Rab-GTPs on Intracellular Membranes

Membrane	Rab-GTPs (Rab Protein)
Cell membrane	Rab5A
Clathrin-coated vesicles	Rab5A
Synaptic vesicles	Rab3A
RER	Rab1, Rab18
cis-Golgi	Rab1 and Rab2
Medial Golgi	Rab6
trans-Golgi	Rab6
Recycling endosomes	Rab4 and Rab11
TGN	Rab9
Early endosomes	Rab5C and Rab8
Late endosomes	Rab7 and Rab9
Lipid droplets	Rab18

GTP, guanosine triphosphate; RER, rough endoplasmic reticulum; TGN, *trans*-Golgi network.

8. **Lysosomes**
   a. **Structure.** Lysosomes are dense membrane-bound organelles that stain for **acid phosphatase** and function to degrade unnecessary cytoplasmic material. Lysosomes possess special sugar-associated membrane proteins on their luminal aspects that shield them from the 50 or so types of acid hydrolases housed in this organelle. Moreover, lysosomal membranes are also rich is cholesterol and **lysobisphosphatidic acid**, where the latter is believed to protect the lysosomal membrane from autodigestion. Furthermore, ATP-powered proton pumps in the lysosome membrane maintain an **acid pH** (<5).
   b. **Formation.** Lysosomes are formed when a vesicle with endocytosed material fuses with a **late endosome**, and enzymatic degradation begins. Formation of a lysosome via one lysosomal pathway (see Fig. 1.12) involves the following intermediates:
      (1) **Early endosomes**
         (a) These irregular vesicles, also known as the **compartment for uncoupling of receptors and ligands (CURL)**, near the cell periphery form part of the pathway for receptor-mediated endocytosis and contain receptor–ligand complexes.
         (b) Their acidic interiors (pH $<$ 6), maintained by ATP-driven proton pumps, aid in the uncoupling of receptors and ligands; receptors return to the cell membrane and ligands move to a late endosome.
      (2) **Late endosomes**
         (a) Late endosomes, irregular vesicles (pH $<$ 5.5) deep within the cell, receive ligands via microtubular transport of vesicles from early endosomes. They contain **both lysosomal proenzymes** (**inactive acid hydrolases**) **and lysosomal membrane proteins**; these are formed in the RER as proenzymes, transported to the Golgi complex for processing, and delivered in separate vesicles to late endosomes.
         (b) These lysosomal proteins and proenzymes are folded in such a fashion within the RER that they display a unique **signal region** that becomes modified in the Golgi apparatus to accept **mannose-6-phosphate** (**M-6-P**), which is inserted into the signal region within the TGN. The presence of M-6-P ensures that they will be packaged specifically into those vesicles that are destined for early and late endosomes, organelles whose membranes possess **M-6-P receptors**.
         (c) Once late endosomes have received a full complement of lysosomal enzymes, they begin to degrade their ligands and are classified as **lysosomes**.
   c. **Types of lysosomes** (Fig. 1.15). Lysosomes are named after the content of recognizable material; otherwise, the general term **lysosome** is used.
      (1) **Multivesicular bodies** are formed by fusion of an early endosome containing endocytic vesicles with a late endosome.
      (2) **Phagolysosomes** are formed by fusion of a **phagocytic vacuole** with a late endosome or a lysosome.

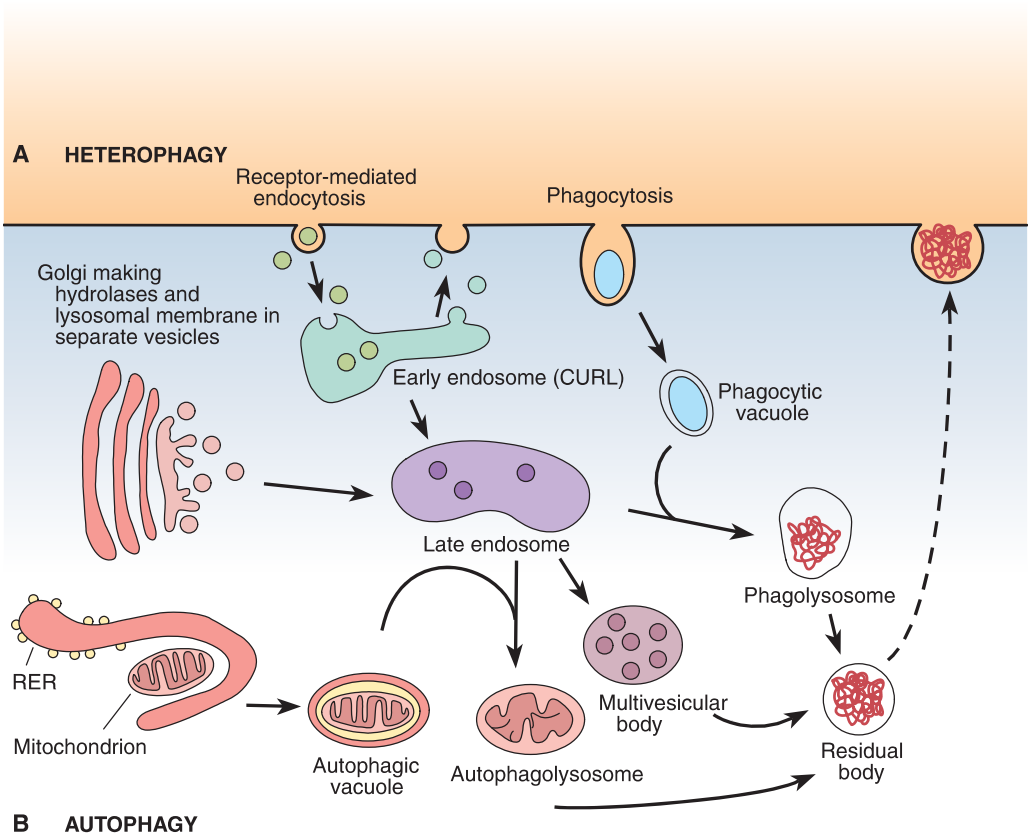


FIGURE 1.15. Heterophagy refers to the intracellular digestion of material taken into the cell from outside (**A**), whereas autophagy is the digestion of parts of the cell itself (**B**). The different pathways and the types of lysosomes involved in each pathway are shown. CURL, compartment for uncoupling of receptors and ligands; RER, rough endoplasmic reticulum.

(3) **Autophagolysosomes** are formed by fusion of an **autophagic vacuole** (Fig. 1.16) with a late endosome or lysosome. Autophagic vacuoles are formed when cell components targeted for destruction become enveloped by smooth areas of membranes derived from the RER.

(4) **Residual bodies** are lysosomes of any type that have expended their capacity to degrade material. They contain **undegraded material** (e.g., lipofuscin and hemosiderin) and eventually may be excreted from the cell.

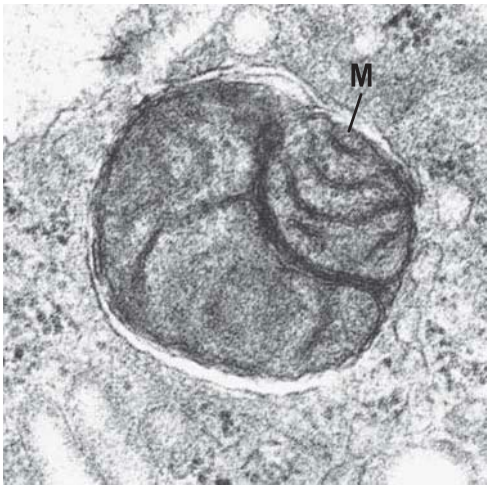


FIGURE 1.16. Electron micrograph of an autophagic vacuole containing mitochondria (M). Once an autophagic vacuole fuses with a late endosome or lysosome (to form an autophagolysosome) further digestion occurs, making the organelles inside unrecognizable and resulting in a structure identified simply as a lysosome.

9. **Peroxisomes** (Fig. 1.9)
   a. **Structure. Peroxisomes** (**microbodies**; 0.15–0.25 μm in diameter) are membrane-bound, spherical, or ovoid organelles that are characterized by the presence of the enzyme **catalase**. Peroxisomes may contain a **nucleoid** (absent in human cells), a crystalline core consisting of urate oxidase (uricase).
   b. They originate from preexisting peroxisomes, which grow by importing specific cytosolic proteins that are recognized by a family of receptor proteins (called **peroxins**) in the peroxisomal membrane. Then the peroxisome divides by fission; it has a life span of approximately 5 to 6 days.
   c. **Function.** Peroxisomes contain various **enzymes** whose numerous functions include the oxidation of long-chain fatty acids, the synthesis of cholesterol, formation of acetyl coenzyme A, and the detoxification of substances such as ethanol. Ethanol degradation forms H_2O_2, a molecule exceptionally harmful to cells. However, the enzyme catalase, composed of four **apocatalase** molecules each of which binds a **heme**, catalyzes the breakdown of H_2O_2 into water. Other peroxisomal enzymes initiate the process of **plasmalogen** synthesis, the major phospholipid component of myelin.

CLINICAL CONSIDERATIONS

Peroxisomal diseases

Zellweger syndrome is a genetic disease in which normal peroxisomes are absent. Infants with this syndrome have profound neurologic disorders and liver and kidney problems and usually die within a few months. Electron micrographs of biopsies from these patients reveal empty peroxisomes, lacking enzymes. Although peroxisomal enzymes may be synthesized, they become dislocated in the cytosol.

Adrenoleukodystrophy is caused by the inability of peroxisomes to metabolize fatty acids. Therefore, lipids accumulate in the nervous system and adrenal glands, impairing their function.

Plasmalogen deficiency has been suggested as a possible contributing factor to the incidence of trisomy 21 and Alzheimer disease as well as in syndromes involving malformed myelin sheaths.

10. **Proteasomes** are discussed in the section "Intracellular digestion" in this chapter.

B. Inclusions. Inclusions are accumulations of materials that are **not metabolically active**. They usually are present in the cytosol only **temporarily**.

1. **Glycogen** appears as small clusters (or in hepatocytes as larger aggregates, known as **rosettes**) of electron-dense 20- to 30-nm β-particles that resemble but are larger than ribosomes. Glycogen clusters are not bound by a membrane but frequently lie close to the SER. Glycogen serves as a **stored energy source** that can be degraded to glucose.
2. **Lipid droplets** vary markedly in size and appearance depending on the method of fixation, and they are not bound by a membrane. Lipid droplets are storage forms of **triglycerides** (an energy source) and **cholesterol** (used in the synthesis of steroids and membranes).
3. **Lipofuscin** appears as membrane-bound, electron-dense granular material varying greatly in size and often containing lipid droplets. Lipofuscin represents a residue of undigested material present in residual bodies (lysosomes of any type that have expended their capacity to degrade material). Because the amount of this material increases with age, it is called **age pigment**. It is most common in nondividing cells (e.g., cardiac muscle cells, neurons) but is also found in hepatocytes.
4. **Crystals** are infrequent in most mammalian cells with the notable exception of the testes, where Sertoli cells house **crystals of Charcot-Böttcher** and interstitial cells contain **crystals of Reinke**.

C. Cytoskeleton. The **cytoskeleton**, the structural framework within the cytosol, functions in maintaining cell shape, stabilizing cell attachments, facilitating endocytosis and exocytosis, and promoting cell movement. Its components include microtubules, centrosome, actin filaments, intermediate filaments, and plectin.

1. **Microtubules**
   a. **Structure.** Microtubules are straight, hollow tubules (25 nm in diameter) composed of **tubulin**. Their rigid wall is composed of 13 protofilaments, each of which consists of a linear arrangement

of **tubulin dimers**; each dimer consists of **α- and β-tubulin subunits** that are linked end-to-end, so that an α-tubulin subunit of one dimer is linked to the β-tubulin subunit of the next dimer.

b. Microtubules are **polar**, in that they have a **plus end** (β-tubulin end) and a **minus end** (α-tubulin end). Polymerization (assembly) and depolymerization (disassembly) occur preferentially at the plus end, but only when **GTP**, in the presence of magnesium ions, is bound to tubulin dimers. The minus end of a microtubule is usually not free but is affixed to the microtubule-organizing center (MTOC).

c. **Microtubules** have **microtubule-associated proteins** (MAPs), such as MAP1, MAP2, MAP3, MAP4, and MAP tau, and Lis 1, which stabilize them, control their lengthening, and bind them to other cytoskeletal components and organelles.

CLINICAL CONSIDERATIONS

Individuals who do not possess the Lis 1 MAPs are born with smooth cerebral hemispheres, a condition known as **lissencephaly**. Children with this condition rarely survive past 15 years of age and display various grades of intellectual disability. Those most severely affected die during the first few months of life.

d. Microtubules also are associated with **kinesin** and **cytoplasmic dynein**, two force-generating proteins (**motor proteins**) that serve as motors for vesicle or organelle movement. Kinesin moves cargo toward the plus end of the microtubule (outward, toward the cell periphery), whereas cytoplasmic dynein moves it toward the minus end (inward, toward the center of the cell).

e. **Function.** Microtubules maintain cell shape; aid in the transport of macromolecules, vesicles, and organelles within the cytosol; assemble into the mitotic spindle during mitosis and ensure the correct distribution of chromosomes to daughter cells; and assist in the formation of cell appendages called cilia and flagella, which beat rhythmically and precisely.

2. Centrosome (MTOC) and centrioles (Fig. 1.17)

a. **Structure.** The **centrosome**, located in the vicinity of the nucleus, is composed of two **centrioles** and an amorphous **pericentriolar cloud**. The centrioles are a pair of cylindrical rods (each

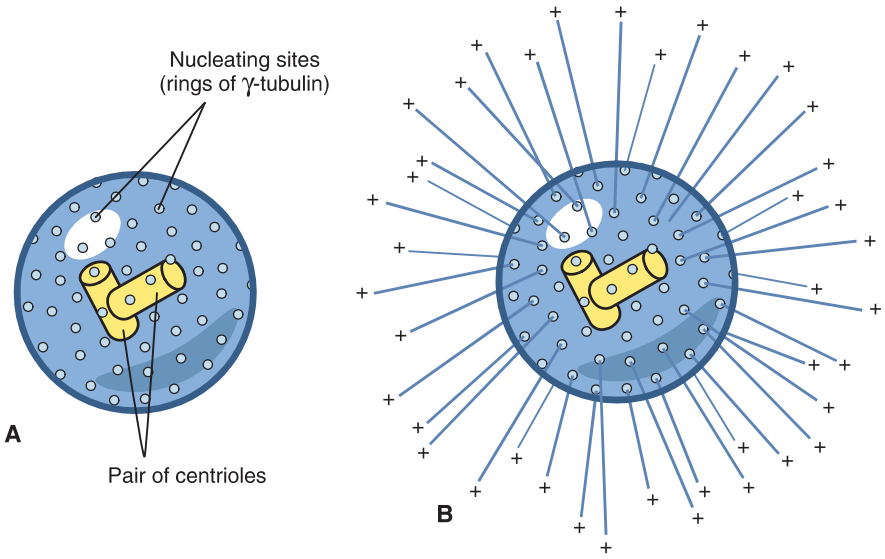


FIGURE 1.17. Polymerization of tubulin at a centrosome. **(A)** A centrosome consists of an amorphous cloud of material containing γ-tubulin rings that initiate microtubule polymerization. Within the cloud is a pair of centrioles. **(B)** A centrosome with attached microtubules. The minus end of each microtubule is embedded in the centrosome, having grown from a nucleating ring, whereas the plus end of each microtubule is free in the cytoplasm. (Modified from Alberts B, Bray D, Johnson A, et al. *Essential Cell Biology*. New York, NY: Garland Publishing; 1998:521.)

0.2 μm wide and 0.5 μm long) positioned at right angles to one another. Each member of the pair is composed of nine triplets of microtubules arranged radially in the shape of a pinwheel and sports a narrow ring of unknown material surrounding their distal ends (the ends away from the nucleus), known as the **distal ring**. The two centrioles of the pair differ from each other because the **mature centriole** was formed in an earlier predecessor of the present cell and is therefore older. The younger centriole is referred to as the **immature centriole**. The mature centriole possesses structures of unknown function known as **appendages** that are associated with the distal ring and **satellites** projecting from the centriole's distal aspect. The proximal ends of both mature and immature centrioles are connected to the nuclear envelope by an uncharacterized proteinaceous material.

b. During the S phase of the cell cycle the centrioles **self-duplicate**, by each parent centriole, forming a **procentriole** at right angles to itself.

c. Centrioles also form **basal bodies**, which appear identical to unpaired centrioles and give rise to the **axonemes** of cilia and flagella.

d. Function

(1) The **centrosome** is the major **MTOC** in the cell.

(2) The **pericentriolar cloud** is composed of hundreds of ring-shaped **γ-tubulins**, where each ring serves as a starting point for the polymerization of one microtubule.

(3) Centrioles play no role in nucleating microtubules, but they help to maintain the organization of the centrosome.

(4) The centrosome itself is also duplicated during the S phase of the cell cycle, and then separates to form the poles of the mitotic spindle, where microtubules originate and converge.

3. Actin filaments (microfilaments)

a. Structure. Actin filaments (7 nm in diameter), composed of globular actin monomers (**G actin**) linked into a **double helix** (F actin), are thin, flexible, and abundant in cells.

b. Actin filaments display **polarity** similar to that of microtubules; that is, their polymerization and depolymerization occur preferentially and more rapidly at the **plus end** (**barbed end**) than at the **minus end** (**pointed end**). Free G actin subunits possess ATP bound to them; when they bind to the growing actin filament, the subunit acts as an enzyme that hydrolyzes ATP, releasing energy. The resultant ADP becomes buried deep in the groove of the filament, and the filament lengthens. During the lengthening of the actin filament, the speed of ATP dephosphorylation increases. When G actin monomers are removed from the minus end, they have ADP attached to them, and, in the cytosol, the nucleotide becomes phosphorylated to ATP.

c. Many **actin-binding proteins** associate with G actin and F actin and are able to accelerate or decelerate the lengthening or shortening of the actin filament as well as permit its branching (Table 1.6). During filament formation, actin monomers are added to the plus end and may be removed from the minus end. In certain conditions, known as **treadmilling**, the same number of G actin monomers is added to the plus end as is removed from the minus end.

table **1.6** Selected Actin-Binding Proteins and Their Functions

Actin-Binding Protein	Function
Formin	Facilitates filament formation and stays attached to the growing end of the filament
ARP complex	Stays attached to the minus end and permits the formation of a lattice work of actin filaments by facilitating branching of actin filaments
Profilin	Attaches to G actin subunits and increases the rate of filament formation
Thymosin	Attaches to G actin subunits and prevents them from binding to the actin filament
Cofilin	Attaches to the minus end of the actin filament and enhances the process of filament shortening
Gelsolin	Cleaves the filament and remains bound to the plus end
Tropomyosin	Increases filament stability and, in striated muscle, masks the active binding site to myosin
Capping protein	Stabilizes the filament and maintains its length by preventing the addition or deletion of G actin subunits
Fimbrin	Assists in the formation of actin filament bundles
α-Actinin	Assists in the formation of actin filament bundles

ARP, actin-related protein.

d. Actin filaments are abundant at the periphery of the cell, where they are anchored to the cell membrane via one or more intermediary proteins (e.g., α-actinin, vinculin, talin).

e. **Function.** Actin filaments act in many **cellular processes**, such as establishing focal contacts between the cell and the extracellular matrix, locomotion of nonmuscle cells, formation of the contractile ring (in dividing cells), formation of a rigid core of microvilli, and the folding of epithelia into tubes during development.

4. **Intermediate filaments** (8–10 nm in diameter) constitute a population of heterogeneous filaments that are the products of at least 70 different genes. In spite of their diversity, intermediate filaments have numerous common characteristics, namely that their basic unit is a **monomer**, composed of a rod-shaped protein whose longest region is an alpha helical structure, the **central domain**, with a globular N-terminal (**head**) and a globular C-terminal (**tail**). Two of these monomers coil around each other to form a dimer. Two dimers assemble head to tail, in an antiparallel, staggered **tetramer formation**. Eight tetramers assemble side by side and are compressed into **unit length filaments** (**ULFs**) that form 10 nm subunits. Many ULFs assemble end-to-end to form the mature intermediate filaments. Although intermediate filaments were formerly believed to be rigid in nature, they have been demonstrated to move and change their shapes, and they may be stretched to a certain extent without breaking. Four types of intermediate filaments exist in the cytoplasm and one type is located in the nucleus as well as a special type located only in the cytoplasm of the cells of the lens of the eye (Table 1.7). In general, intermediate filaments **provide mechanical strength** to cells; they lack polarity and do not require GTP or ATP for assembly, which occurs along the entire length of the filament.

5. **Plectin** is a 500-kDa protein that has a ubiquitous presence in most cells. It acts to attach microfilaments, intermediate filaments, and microtubules to each other, thereby providing a very stable configuration to the cytoskeleton. Plectin is also present in striated muscles and assists desmin, a muscle-specific intermediate filament, in maintaining the regular arrangement of myofibrils. Additionally, plectin has been shown in reinforcing the cell–cell junctions by binding some of the structural molecules to the cytoskeleton.

table 1.7 Major Types of Intermediate Filaments

Type	Protein	Location	Function
I II	Acidic keratins Basic keratins	Various types of epithelial cells	They are the tonofilaments associated with desmosomes and hemidesmosomes; in nails and hair they are known as trichocytic (hard) keratins
III	Vimentin*	Endothelial cells, leukocytes, fibroblasts	Architectural support for cell membranes; fix organelles in position
	Desmin†	Muscle cells	Links myofibrils to each other at Z disks
	GFAP†	Glia and astrocytes	Provides structural support
	Peripherin	Axons of peripheral nervous system (PNS)	It may assist in the elongation of axons
	Synemin	Muscle cells	Binds to α-actinin and desmin
IV	NF-L (70 kDa)‡	Axons of neurons	NF-L, NF-M, and NF-H all function to provide support for axons and establish the axon diameter
	NF-M (140 kDa)‡	Axons of neurons	
	NF-H (210 kDa)‡	Axons of neurons	
	Nestin	Developing neurons and glia	Provides support for embryonic cells and is not present in mature cells
	α-Internexin	Axons of neurons	Copolymerizes with the other neurofilaments
	Syncoilin	Muscle	Binds to desmin
V	Nuclear lamins A, B, and C	Nuclei of all human cells	Forms a two-dimensional meshwork, the nuclear lamina, deep to the inner nuclear membrane to organize the peripheral nuclear chromatin; also form the framework of the nucleoplasm
VI	Phakinin and filensin**	Lens fiber cells of the eye	These beaded filaments of the lens fibers of the eye maintain lens transparency

GFAP, glial fibrillary acidic protein.

*Vimentin is the most common intermediate filament with a wide distribution.

†Desmin and GFAP may copolymerize with vimentin; they are sometimes categorized as vimentin-like filaments. Vimentin is the most commonly found intermediate filament in a variety of cells.

‡NF-L (neurofilaments light), NF-M (neurofilaments medium), and NF-H (neurofilaments heavy). NF-L copolymerizes to form neurofilaments with either NF-M or NF-H.

**Phakinin and filensin copolymerize to form beaded filaments. They are found only in the lens fiber cells of the eye.

CLINICAL CONSIDERATIONS

Tumor diagnosis is often based on immunocytochemical identification of the intermediate filaments in the tumor cells because the type of intermediate filament present identifies the tissue from which the metastatic cancer cells originated. For example, an undifferentiated tumor that has metastasized to a bone can be identified as a carcinoma (of epithelial origin) if it stains with cytokeratin antibody in immunocytochemistry.

VIII. ORGANELLE INTERACTIONS

Organelles are involved in all cellular processes, including the uptake and release of material by cells, protein synthesis, and intracellular digestion. These various interactions provide the basis for a functional approach to examine some dynamics of cell biology.

A. Uptake and release of material by cells

1. **Endocytosis**, the **uptake** (**internalization**) of material by cells, includes pinocytosis, receptor-mediated endocytosis, and phagocytosis.
   a. **Pinocytosis** ("**cell drinking**") is a *nonspecific* (*random*) uptake of extracellular fluid and material in solution into **pinocytic vesicles**.
   b. **Receptor-mediated endocytosis** is the *specific uptake* of a substance (**ligand**), such as low-density lipoproteins (LDLs) and protein hormones, by a cell that has a cell membrane receptor for a particular ligand. It involves the following sequence of events (see Fig. 1.12):
      (1) Ligands **bind specifically** to their receptors on the cell surface forming **ligand–receptor complexes** that cluster into a **clathrin-coated** pit, which forms a clathrin-coated vesicle containing the ligands.
      (2) The cytoplasmic clathrin coat is rapidly **lost**, leaving an **uncoated endocytic vesicle** containing the ligand that fuses with an early endosome.

CLINICAL CONSIDERATIONS

Familial hypercholesterolemia is associated with a decreased ability of cells to take in cholesterol, which normally is ingested by receptor-mediated endocytosis of LDLs. This disease is caused by an inherited genetic defect that results in an inability to synthesize LDL receptors or in the synthesis of defective receptors unable to bind either to LDLs or to clathrin-coated pits. It is characterized by an elevated level of cholesterol in the bloodstream. This facilitates early development of **atherosclerosis**, which may be fatal.

   c. **Phagocytosis** ("**cell eating**") is the internalization of microorganisms, other cells, and/or particulate matter (frequently of foreign origin) by cells, such as **macrophages** and **neutrophils**, usually with the aid of cell surface receptors.
      (1) A macrophage binds via its **Fc receptors** to a bacterium coated with the antibody immunoglobulin G or via its C3b receptors to a complement-coated bacterium.
      (2) Binding progresses until the cell membrane completely envelops the bacterium, forming a phagocytic vacuole that fuses with an early endosome or a phagolysosome.
2. **Exocytosis** is the **release of material** from the cell via fusion of a secretory granule membrane and the cell membrane. It requires interaction of receptors of the secretory granule membrane and of the cell membrane as well as the **coalescence** (adherence and joining) of the two phospholipid bilayers. Exocytosis takes place in both regulated and constitutive secretion.
   a. **Regulated secretion** (**signal-directed secretion**) is the release of materials (e.g., neurotransmitters, enzymes) **stored** in the cell, in response to an **extracellular signal**.
   b. **Constitutive secretion** (**default pathway**) is the more or less **continuous** release of material (e.g., collagen and plasma proteins) without any intermediate storage step. An extracellular signal is **not** required for constitutive secretion.
3. **Membrane recycling** maintains a relatively constant cell membrane surface area following exocytosis. In this process, the secretory granule membrane added to the cell membrane during

exocytosis is **retrieved** through endocytosis via clathrin-coated vesicles. This membrane is returned to the TGN via early endosomes for further recycling. Figure 1.18 illustrates endocytic pathways used by cells. More specific information concerning the mechanisms of membrane recycling and transference was presented in earlier sections of this chapter (see Section 7, "Coated vesicles").

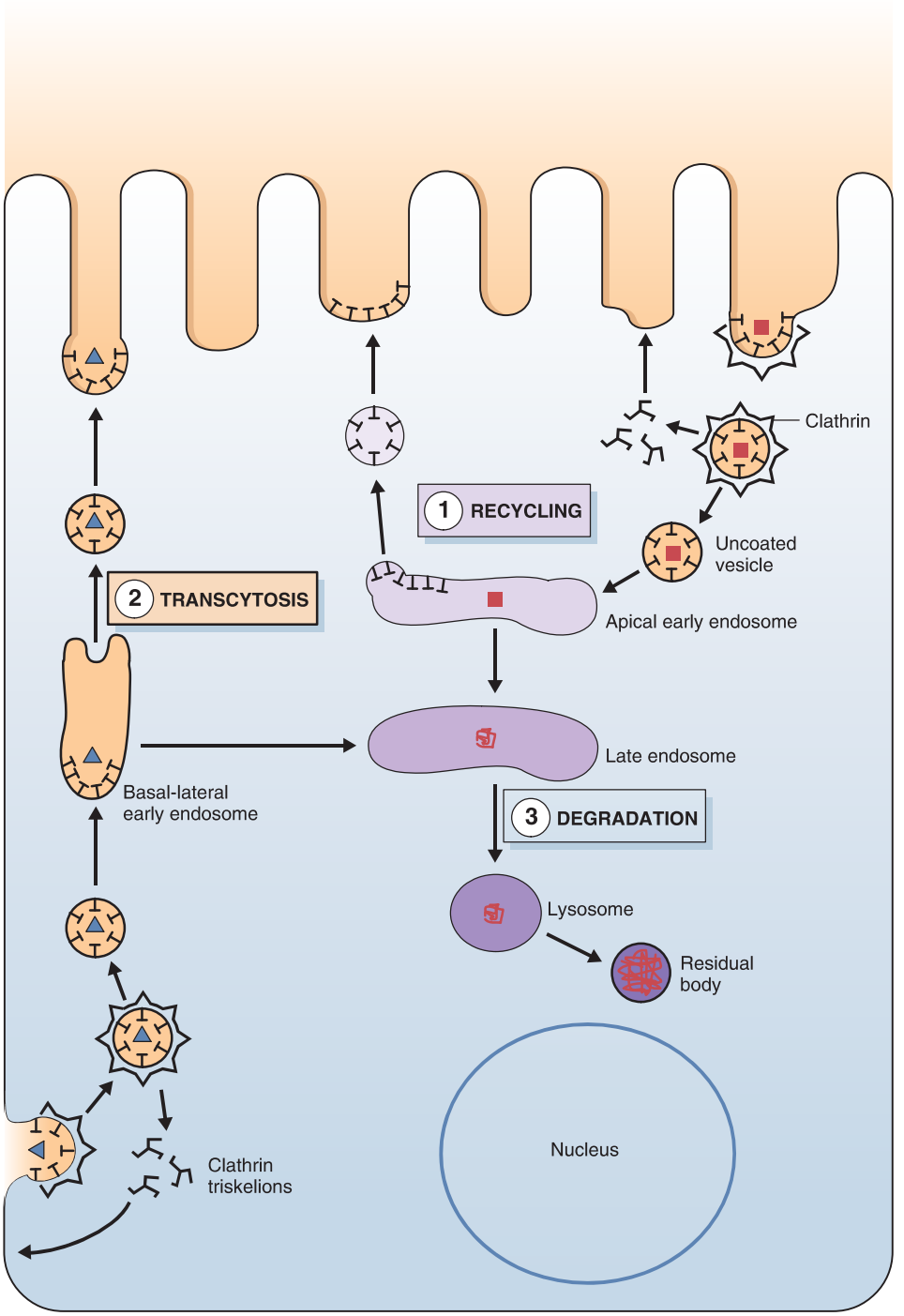


FIGURE 1.18. Pathways used by receptors and ligands following endocytosis. (1) Recycling of receptors to the same cell membrane surface. (2) Transcytosis from one surface (e.g., basal–lateral) to another (e.g., apical). Transcytosis can occur in either direction, but separate early endosome compartments near the domain of vesicle entry are used. (3) Degradation: If not retrieved from either early endosome compartment, the ligands move to a common late endosome, which subsequently becomes a lysosome, where degradation is completed.

B. Protein synthesis

1. **Synthesis of membrane-packaged proteins** involves translation of mRNAs encoding the protein on polyribosomes at the surface of the RER, transport of the growing polypeptide chain across the RER membrane and **into the cisterna** (**lumen**), and the processing of the polypeptide/protein within the RER. These water-soluble proteins will be packaged into a vesicle, which buds off from the RER and is then transported into the **lumen** (or interior) **of another organelle** or for **secretion** from the cell.
   a. A three-step process **translates mRNA** as detailed in Figure 1.19. The ribosome moves along the mRNA in the 5′ to 3′ direction using acylated tRNAs as adapters to add each amino acid to the end of the growing peptide chain, which is always located at the P site of the large subunit of the ribosome.

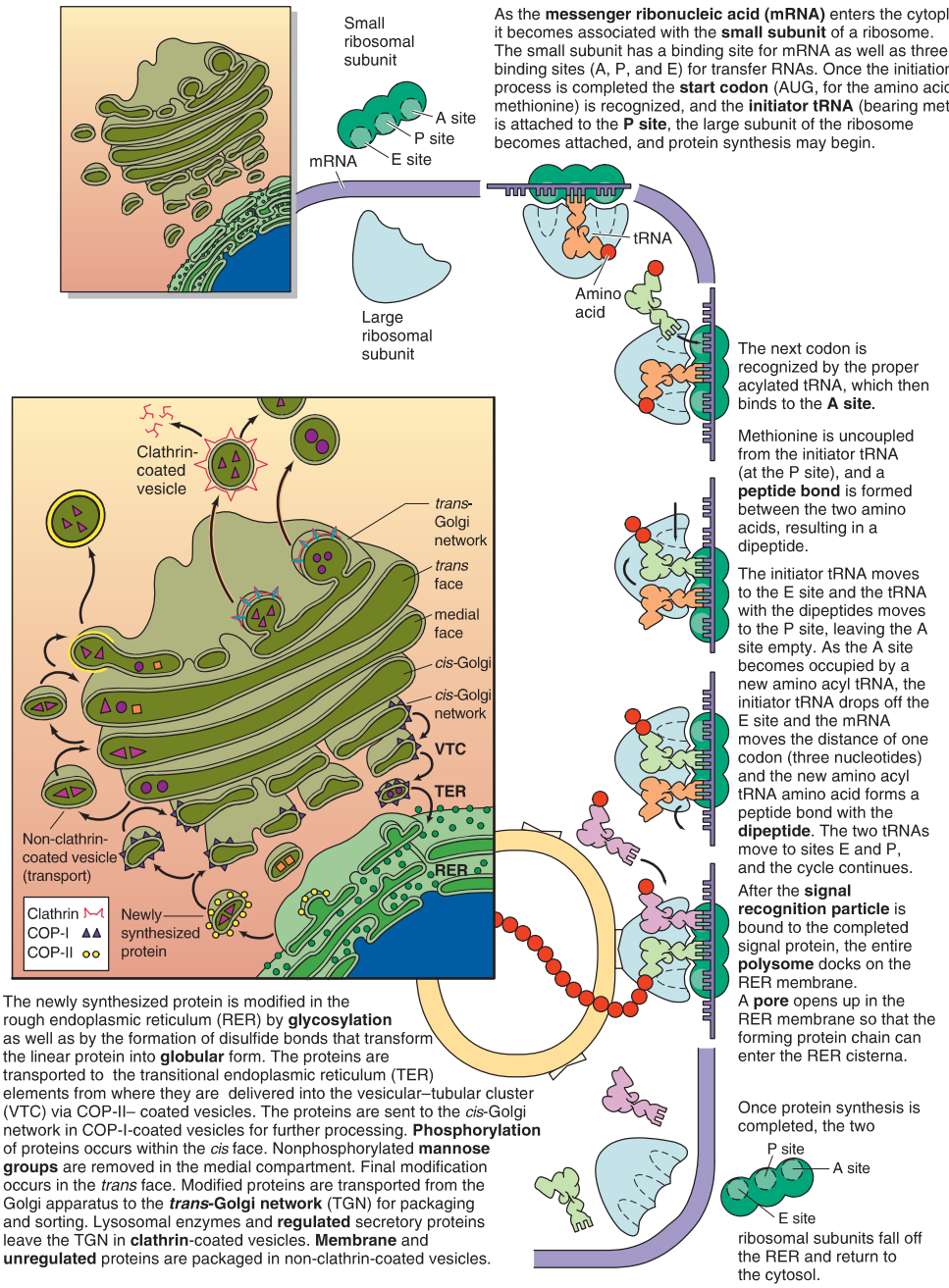


FIGURE 1.19. A diagram illustrating protein synthesis. (From Gartner LP. *Color Atlas of Histology*. 7th ed. Baltimore, MD: Wolters Kluwer; 2018.)

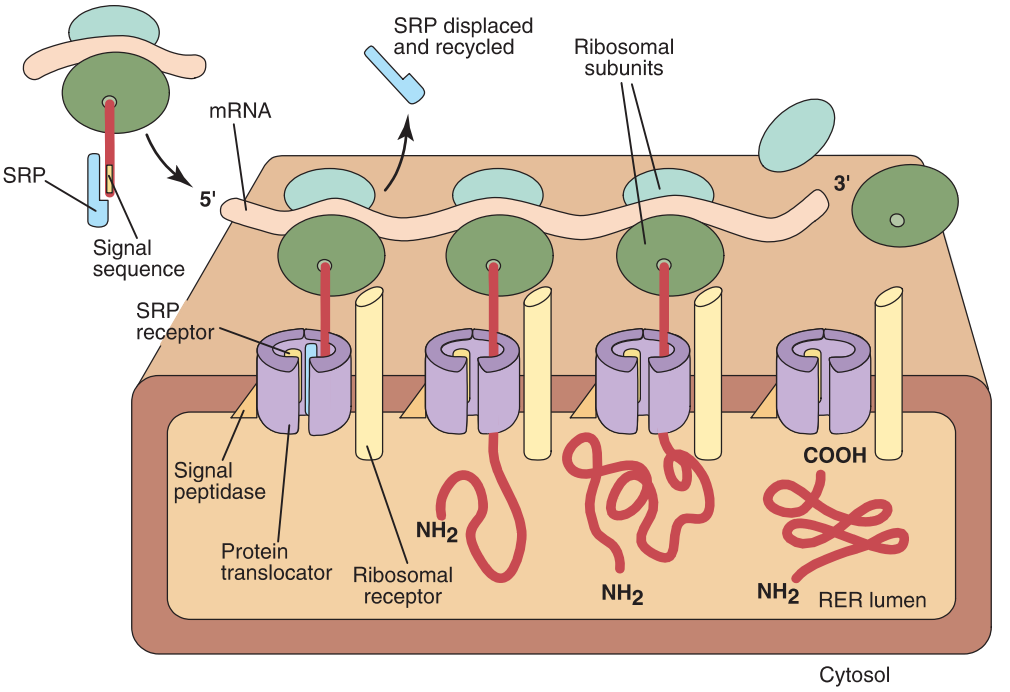


FIGURE 1.20. The signal hypothesis. The signal sequence of a newly formed secretory polypeptide binds to a signal recognition particle (SRP) that delivers the ribosome–peptide–SRP complex to a receptor on the rough endoplasmic reticulum (RER). The SRP is recycled, and the polypeptide is translocated into the cisterna of the RER, where a signal peptidase cleaves off the signal sequence. mRNA, messenger ribonucleic acid.

b. Transport of the newly formed peptide into the RER cisterna occurs by a mechanism described by the **signal hypothesis** as depicted in Figure 1.20.

(1) When the signal sequence is formed on the ribosome, a ribonucleated protein (a complex of RNA and protein) known as the **signal recognition particle** (**SRP**) in the cytosol binds to it, interrupts protein synthesis, and facilitates the relocation of the polysome to **SRP receptors** in the RER membrane.

(2) The large subunits of the ribosomes bind to ribosome receptor proteins in the RER membrane. The SRP detaches, and multisubunit **protein translocators** form a **pore** across the RER membrane. Synthesis resumes, and the newly formed polypeptide is threaded through the pore and into the RER cisterna (lumen).

c. RER posttranslational modification

(1) After the newly formed polypeptide enters the cisterna, a **signal peptidase** cleaves the signal sequence from it.

(2) The polypeptide is glycosylated and disulfide bonds form, converting the linear polypeptide into a globular form.

d. Protein transport from the RER to the *cis*-Golgi (Fig. 1.21)

(1) Transitional elements of the RER give rise to **coatomer-II-coated vesicles** containing newly synthesized protein.

(2) These COP II–coated vesicles move to the **VTC** where they fuse with the membranes to deliver the protein.

(3) The **VTC** acts as a first way station for the segregation of anterograde versus retrograde transport in the secretory pathway. Either proteins move forward toward the ***cis*-Golgi** or, if they are RER-resident proteins that managed to escape from the RER, are captured by a specific membrane receptor protein and returned in **COP-I coatomer–coated vesicles** to the RER along a microtubule-guided pathway.

e. Anterograde transport from the VTC to the *cis*-Golgi is via COP-II-coated vesicles.

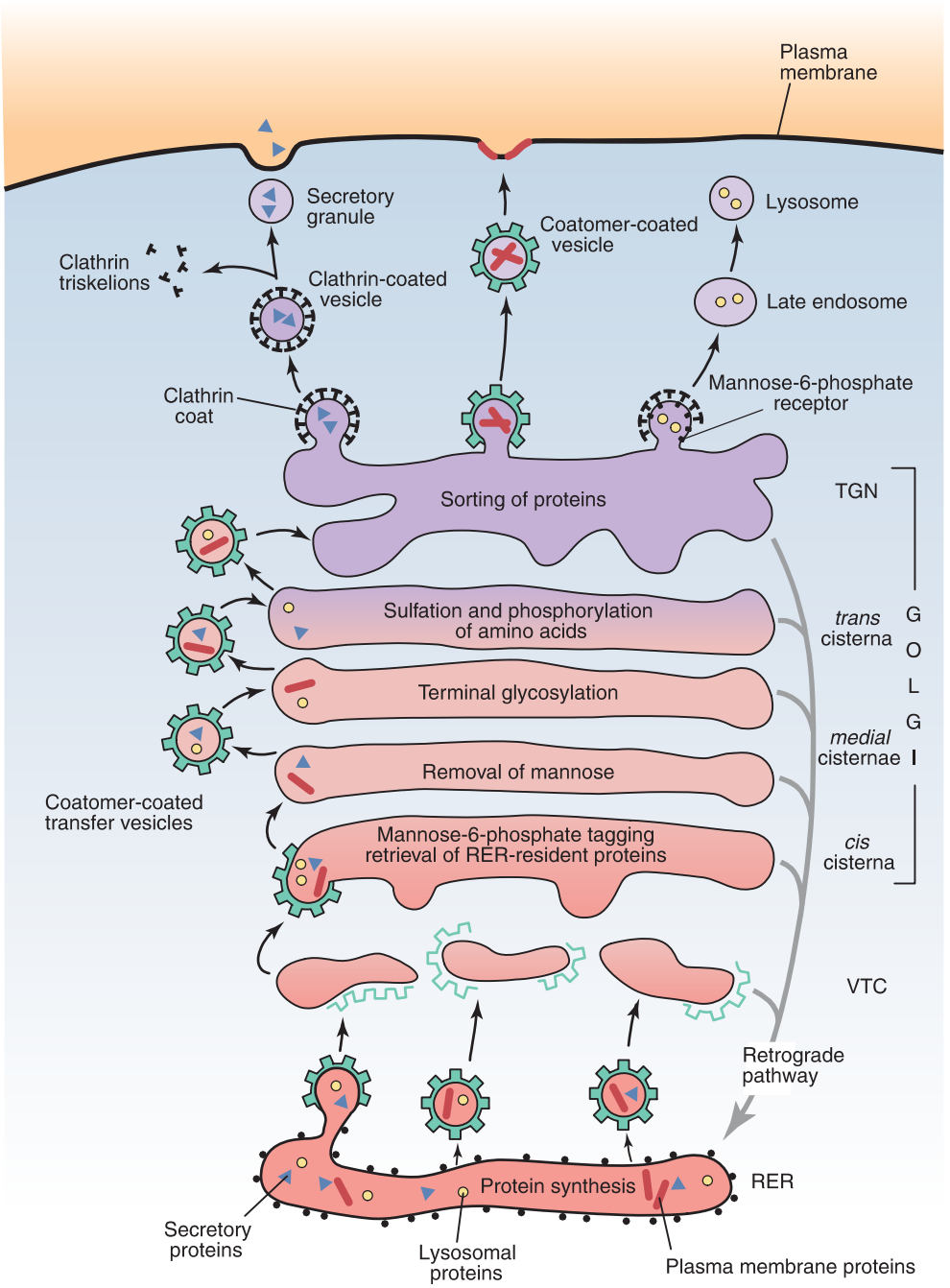


FIGURE 1.21. The pathways of secretory proteins in separate compartments of the Golgi complex. Proteins synthesized in the rough endoplasmic reticulum (RER) include secretory (▲), membrane (/), and lysosomal (o) proteins. These proteins bud off the transitional element of the RER via COP-coated vesicles and enter the vesicular–tubular cluster (VTC). From here they are transported to the *cis*-Golgi via COP-coated vesicles. Anterograde passage through the Golgi cisternae is either via COP-coated vesicles or by cisternal maturation. Cisternal maturation coupled with retrograde vesicular transport of Golgi enzymes is currently a favored view. Only COP-I vesicles are thought to function in retrograde transport (from Golgi to VTC or RER), but both COP-II and COP-I may function in anterograde transport. Not all proteins undergo all of the chemical modifications (e.g., only lysosomal proteins undergo tagging with mannose-6-phosphate). Final sorting occurs in the *trans*-Golgi network (TGN).

f. **Movement of material anterograde among the Golgi subcompartments** may occur by cisternal maturation and/or by vesicular transport, as follows:
   (1) Cisternae containing proteins may change in biochemical composition as they move intact across the stack.
   (2) Vesicles (COP-II-coated, according to some investigators) may bud off one cisterna and fuse with the dilated rim of another cisterna.
   (3) Although both mechanisms have been observed, the precise way that anterograde transport occurs across the Golgi stack of cisternae is unresolved.
   (4) **Retrograde** vesicular transport occurs between Golgi cisternae and between the Golgi and the VTC or RER via COP-I-coated vesicles.

g. **Protein processing in the Golgi complex** occurs as proteins move from the *cis* to the *trans* face of the Golgi complex through **distinct cisternal subcompartments**. This process is described in Figure 1.21.

h. **Final sorting of proteins in TGN** (see Fig. 1.21):
   (1) **Regulated secretory proteins** are sorted from membrane and lysosomal proteins and delivered via clathrin-coated vesicles to condensing vacuoles, in which removal of water via ionic exchanges yields **secretory granules**.
   (2) **Lysosomal proteins** are sorted into clathrin-coated regions of the TGN that have receptors for M-6-P and are delivered to late endosomes via clathrin-coated vesicles.
   (3) **Cell membrane proteins** are sorted into coatomer-coated regions of the TGN and delivered to the cell membrane in COP-II coatomer–coated vesicles.

2. **Synthesis of transmembrane proteins** also takes place on polyribosomes at the surface of the RER, but rather than entering the RER lumen, the transfer process is **halted** (by a **stop-transfer sequence**), and the transmembrane protein becomes anchored in the RER membrane. The ultimate destination of this protein will be the RER membrane, the membrane of another organelle, or the cell membrane.
3. **Synthesis of cytosolic proteins** takes place on **free** polyribosomes in the cytosol and is directed by mRNAs that **lack** signal codons. Such proteins (e.g., protein kinase and hemoglobin) are released directly into the cytosol.

C. Intracellular digestion

1. **Nonlysosomal digestion** is the degradation of cytosolic constituents by mechanisms outside of the vacuolar lysosomal pathway. The major site for the degradation of unwanted, damaged, malformed, or incorrectly folded proteins is the **proteasome**, a cylindrical complex of nonlysosomal proteases. Before a protein can enter the proteasome, it must be marked for destruction by becoming enzymatically tagged with **ubiquitin**, a relatively small protein 76 amino acids long that is a common occupant of the cytoplasm and of the nucleus. This **ubiquitination** delivers proteins to the proteasome, where they are broken down to small peptides, 7 to 8 amino acids long.
   a. Each proteasome is a 26S nonmembranous, cylindrical organelle with a hollow center; it is composed of three subunits, a 20S **core particle** and two **regulatory particles**, 19S each, capping each end (entry face [top] and exit face [bottom]) of the proteasome. The core particle is 15 nm tall with a diameter of 11 to 12 nm whose central lumen may be as small as 1.3 nm or as large as 5.3 nm in diameter. Viewed from the side, the core particle is seen to be composed of four ring-shaped units, named α, β, β, and α, counting from entry face to exit face. The two α-subunits bind the regulatory particles, whereas the luminal aspects of the two β-subunits function as proteolytic enzymes. The regulatory subunit at the entry face acts as a lid that controls access to the lumen of the proteasome, whereas the regulatory subunit on the exit face permits the release of the products of proteolysis (Fig. 1.22).
   b. The process of ubiquitination requires a set of three enzymes that attach a ubiquitin molecule to the targeted protein. The first enzyme, **ubiquitin-activating enzyme** (**E1**), activates ubiquitin so that the second enzyme, **ubiquitin-conjugating enzyme** (**E2**), can bind to the targeted protein. The third enzyme, **ubiquitin-ligase** (**E3**), can now transfer the ubiquitin molecule

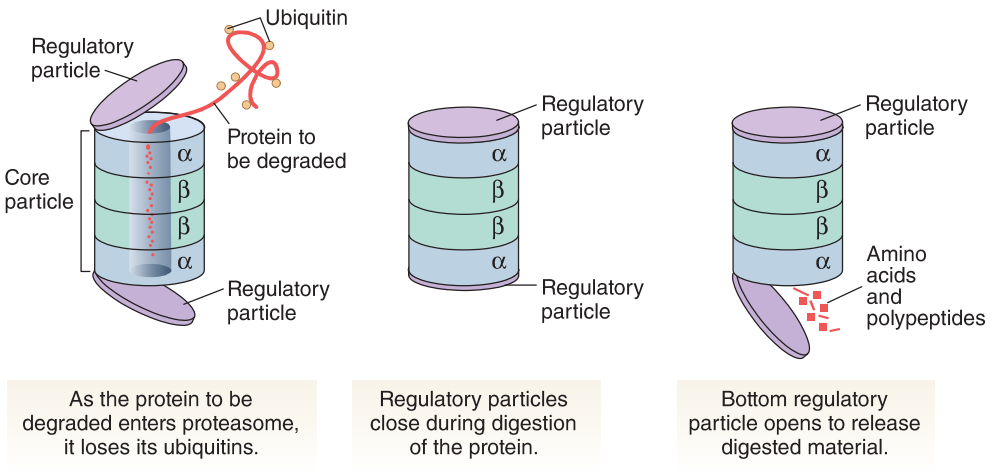


FIGURE 1.22. Proteasome degrading a ubiquinated protein.

to the targeted protein. This process is repeated several times, so that a number of ubiquitin molecules may be attached to each other, forming a **polyubiquitin chain** bound to the targeted protein. E1, E2, and especially E3 come in many forms, indicating that recognition of a specific targeted protein is probably enzyme specific.

c. Once the targeted protein is polyubiquitinated (at least four ubiquitin molecules must be bound to the protein) it may bind, in the presence of ATP, to the regulatory particle at the entry face. The regulatory particle unhinges and, similar to a lid that is attached to a pot, lifts to allow the protein access to the lumen of the core particle. However, in order for the protein to be able to enter the narrow lumen of the core particle two things must take place:

(1) the target protein must be deubiquitinated and

(2) the target protein must be unfolded, where the unfolding is an energy-requiring process.

d. The unfolded protein is introduced into the lumen of the core particle, a procedure known as **translocation**. The target protein is then degraded by the enzymatic activity of the β-subunits of the proteasome.

Although most proteins must be ubiquinated before they may be selected for entry into the proteasome, certain exceptions exist, especially if the cell is under stressful conditions such as exposure to high temperature, infectious agents, or higher than normal oxygen levels.

2. Lysosomal digestion (see Fig. 1.15) is the degradation of material within various types of lysosomes by lysosomal enzymes. Different lysosomal compartments are involved, depending on the origin of the material to be degraded.

a. Heterophagy is the ingestion and degradation of **foreign material** taken into the cell by receptor-mediated endocytosis or phagocytosis.

(1) Digestion of **endocytosed** ligands occurs in **multivesicular bodies** (see Fig. 1.15).

(2) Digestion of **phagocytosed** microorganisms and foreign particles begins and may be completed in **phagolysosomes**.

b. Autophagy is the segregation of an organelle or other cell constituents within membranes from the RER to form an **autophagic vacuole** (see Fig. 1.16), which is subsequently digested in an **autophagolysosome**.

c. Crinophagy is the fusion of **hormone secretory granules** and lysosomes and their subsequent digestion. Crinophagy is used to remove **excess numbers** of secretory granules from the cell.

CLINICAL CONSIDERATIONS

Lysosomal storage diseases are hereditary disorders caused by a deficiency in specific lysosomal acid hydrolases. Therefore, **lysosomes** are unable to degrade certain compounds, which accumulate and interfere with cell function.

1. **Tay-Sachs disease** is characterized by glycolipids (namely, G_{M2} gangliosides) accumulating in the lysosomes of neurons as a result of a deficiency of the enzyme hexosaminidase A. The disease is most common in children of central European Jewish descent. The large buildup of gangliosides in neurons of the brain results in marked degenerative changes in the central nervous system, and death usually occurs before the age of 4 years.
2. A hallmark of **Hurler syndrome** is that glycosaminoglycans (GAGs) and proteoglycans accumulate in the heart, brain, liver, and other organs. This rare inherited disease is caused by a deficiency in any one of 10 lysosomal enzymes involved in the sequential degradation of GAGs. Clinical features of Hurler syndrome include skeletal deformities, enlarged organs, progressive mental deterioration, deafness, and death before the age of 10 years.
3. **Glycogen storage diseases** (at least 10 distinct types) are caused by a hereditary defect in an enzyme involved in either the synthesis or the degradation of glycogen. As a result, glycogen accumulates most often in the liver, skeletal muscle, and the heart, but the major organ involvement depends on the particular enzymatic defect.

IX. NUCLEUS

A. Structure. The nucleus, the largest organelle of the cell, includes the **nuclear envelope**, **nucleolus**, **nucleoplasm**, and **chromatin** (Fig. 1.23).

B. Function. The nucleus houses the genetic material encoded in the DNA of the chromatin and directs protein synthesis in the cytoplasm via **rRNA**, **mRNA, and tRNA**. All types of RNAs, including **regulatory RNAs (non-coding RNAs)**, are synthesized in the nucleus.

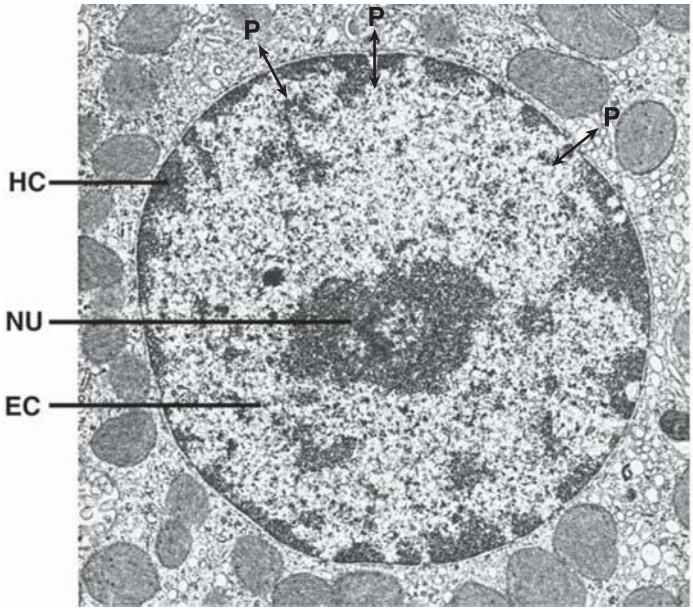


FIGURE 1.23. Electron micrograph of the cell nucleus. The nuclear envelope is interrupted by nuclear pores (P). The inactive heterochromatin (HC) is dense and mostly confined to the periphery of the nucleus. Euchromatin (EC), the active form, is less dense and is dispersed throughout. NU, nucleolus.

X. NUCLEAR ENVELOPE

The nuclear envelope surrounds the nuclear material and consists of two concentric membranes separated from each other by a narrow perinuclear cisterna. These membranes fuse at intervals, forming openings called **nuclear pores** in the nuclear envelope (Fig. 1.24).

A. Outer nuclear membrane

1. This membrane is about 6 nm thick, faces the cytoplasm, and is continuous at certain sites with the RER.
2. A loosely arranged mesh of intermediate filaments (**vimentin**) surrounds the outer nuclear membrane on its cytoplasmic aspect and **ribosomes** stud the outer membrane's cytoplasmic surface. Proteins synthesized on these ribosomes enter the perinuclear cisterna.

B. Inner nuclear membrane

1. The inner nuclear membrane (about 6 nm thick) faces the nuclear material but is separated from it and is supported on its inner surface by the fibrous **nuclear lamina** (80–300 nm thick) that is composed primarily of **lamins A**, **B_1**, **B_2**, and **C**.
2. These intermediate filament proteins form an orthogonal trellis that binds to transmembrane receptor molecules (such as **emerin** and various **lamina-associated polypeptides**) traversing the inner nuclear membrane. The various lamins organize the nuclear envelope, direct the formation of nuclear pore complexes (NPCs), and arrange the perinuclear chromatin. In addition, they are essential during the mitotic events, when they are responsible for the ordered disassembly and reassembly of the nuclear envelope. Phosphorylation of lamins leads to disassembly, and dephosphorylation results in reassembly of the nuclear envelope.

C. Perinuclear cisterna. The **perinuclear cisterna**, located between the inner and outer nuclear membranes (20–40 nm in width), is continuous with the cisterna of the RER.

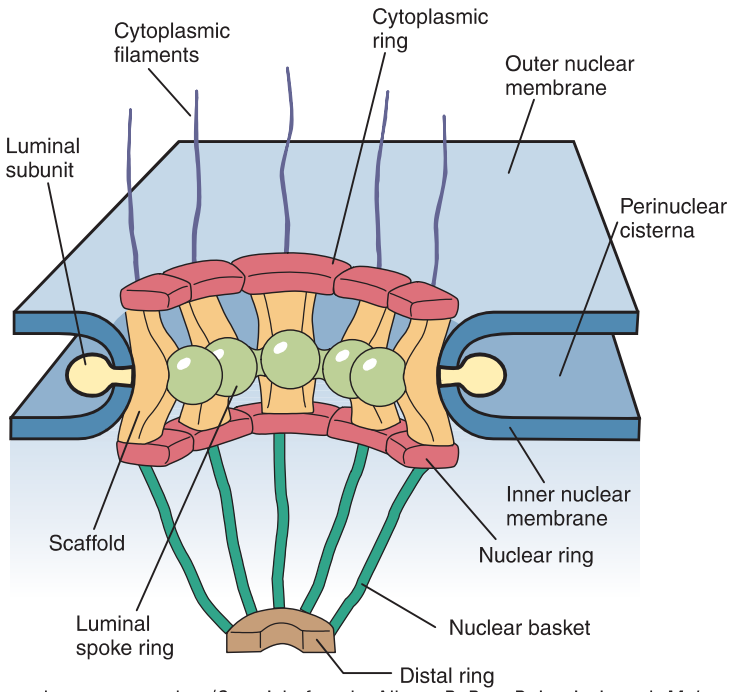


FIGURE 1.24. The nuclear pore complex. (Copyright from by Alberts B, Bray D, Lewis J, et al. *Molecular Biology of the Cell*. 3rd ed. New York, NY: Garland Science; 1994. Adapted with permission from Garland Science/Taylor & Francis LLC.)

D. Nuclear pores

1. **Nuclear pores** (about 80 nm in diameter), formed by fusion of the inner and outer nuclear membranes and associated with the **NPC**, number from dozens to thousands depending upon the metabolic activity of the cell.
2. They permit passage of certain molecules in either direction between the nucleus and the cytoplasm via a 9 nm channel opening.

E. Nuclear pore complex

1. **Structure.** The NPC is composed of nearly 100 proteins (jointly known as **nucleoporins**), some of which are arranged in eightfold symmetry around the margin of the pore. The nucleoplasmic aspect of the pore exhibits a **nuclear basket**, whereas the cytoplasmic aspect displays fibers (**cytoplasmic filaments**) extending into the cytoplasm. The transportation of proteins into and out of the nucleus occurs via **receptor-mediated transport**.
   a. The **cytoplasmic ring**, located around the cytoplasmic margin of the nuclear pore, is composed of eight subunits, each possessing a **cytoplasmic filament** composed of a **Ran-binding protein** (GTP-binding protein) extending into the cytoplasm. These fibers may serve as a staging area for proteins to be transported into the nucleus.
   b. The **nucleoplasmic ring** is located around the nucleoplasmic margin of the nuclear pore and is also composed of eight subunits. Extending from this ring into the nucleoplasm is a basket-like structure, the **nuclear basket**. Attached to the distal end of the nuclear basket is the **distal ring**. This innermost ring assists in the export of RNA, ribosomes, and other substances into the cytoplasm.
   c. The **luminal ring** is interposed between the cytoplasmic and nucleoplasmic rings. Again, eight transmembrane proteins project into the lumen of the nuclear pore, anchoring the complex into the pore rim. The lumen may be a gated channel that impedes passive diffusion. A moiety of each of these transmembrane proteins also projects into the perinuclear cistern.
2. **Function.** The NPC permits passive movement across the nuclear envelope via a 9- to 11-nm open channel for simple diffusion. Most proteins, regardless of size, pass in either direction only by **receptor-mediated transport**. These proteins have clusters of certain amino acids known as **nuclear localization segments** that act as signals for transport.
3. **Transport mechanisms** involve a group of transporter proteins, **exportins** and **importins**. The function of these transporter proteins is regulated by **Ran**, a group of GTP-binding proteins, along with specific **nucleoporins**. Transporter proteins recognize polypeptide sequences on the proteins that are to be transported in one direction or the other. Exportins recognize polypeptide sequences known as **nuclear export sequences** and export molecules bearing them into the cytoplasm, whereas importins recognize **nuclear localization sequences**, and facilitate their import into the nucleus. Transport signals of this type are called **nucleocytoplasmic shuttling signals**.

CLINICAL CONSIDERATIONS

Mutations in the **Huntingtin** (**HTT**) **genes** are responsible for the inherited condition known as **Huntington disease** that affects 10 in 100,000 people of Caucasian descent; men and women are affected equally. This condition usually begins when the patient is between 30 and 50 years of age, but in a small percentage of patients the condition may appear before they reach 20 years of age. The symptoms begin with mood disorders and rapidly progress to loss of muscular coordination resulting in involuntary, erratic movement. Many patients lose the ability to speak and their mental acuity deteriorates to dementia. Most patients die within two decades after the onset of the disease. The most commonly affected cells are the spiny neurons of the striatum in the basal ganglia of the brain and pyramidal neurons in the cerebral cortex and they have been shown to accumulate mutated Huntingtin proteins (coded by the mutated HTT genes) in their nuclei.

Recently, researchers have demonstrated that the mutation affects nucleoporins that cause functional disturbances in the NPCs, which become unable to permit the transport of proteins from the nucleus into the cytoplasm. The accumulated proteins in the nucleus interfere with the functions of the neuron, resulting in this debilitating, lethal condition.

XI. NUCLEOLUS

The nucleolus, a nuclear inclusion that is not surrounded by a membrane, is observed in interphase cells that are actively synthesizing proteins (some nuclei house several nucleoli). It contains mostly rRNA and protein, such as **nucleostemin**, **nucleolin**, and **fibrillarin**, along with a modest amount of DNA. Each nucleolus is formed around the **nucleolar organizer regions** (**NORs**), portions of the chromosomes (in humans, chromosomes 13, 14, 15, 21, and 22) where rRNA genes are located, along with the ribonucleoprotein **SRP** and **RNA polymerase I**, the enzyme required for the transcription of rRNA. Additionally, the presence of 15-nm **maturing ribosomal precursor** particles should be noted because they represent the assembly of the 5.8S, 18S, and 28S rRNA subunits. Ribosomal proteins, manufactured in and imported from the cytoplasm, are combined with rRNA to form the small and large ribosomal subunits, which are then individually exported into the cytoplasm where ribosomal assembly is completed. In order to complete the formation of the large ribosomal subunit the 5S rRNA is also required. However, this is coded by a region of the DNA outside the nucleolus. RNA polymerase III transcribes the 5S rRNA, which is transported into the nucleolus to become incorporated into the large subunit. NORs are also involved in reconstituting the nucleolus during the G_1 phase of the cell cycle. Although it has been demonstrated by electron microscopy that the nucleolus is composed of three to four distinct regions, recent studies have dismissed the importance of these morphologic distributions.

CLINICAL CONSIDERATIONS

Large quantities of a protein in the nucleolus that resembles guanine nucleotide–binding protein, known as **nucleostemin**, are present in cancer cells and stem cells because this protein appears to function in regulating the cell cycle and also has a direct influence on cell differentiation.

The nucleolus also sequesters certain nucleolar proteins, such as nucleostemin, that function as cell cycle checkpoint signaling proteins. These cell cycle regulator proteins remain sequestered in the nucleolus until their release is required for targets in the nucleus and/or the cytoplasm. Additional functions include sensing and repair of damaged DNA, managing the fate of noncoding RNAs, as well as managing responses of cells to various stresses. Following prophase of the cell cycle the nucleolus disintegrates because the NORs of chromosomes 13, 14, 15, 21, and 22 are unavailable for transcription. Subsequent to telophase the NORs unwind and facilitate the reconstitution of the nucleolus.

XII. NUCLEOPLASM AND NUCLEAR PARTICLES

Nucleoplasm is the protoplasm surrounded by the nuclear envelope in which the chromosomes, nucleoli, and various nuclear particles are embedded. It is a viscous matrix composed mostly of water whose viscosity is increased by the various types of macromolecules (some from the NPCs) and ions along with transcriptional processing apparatus that are suspended or dissolved in it. Most authors believe that the nucleoplasm is ordered by the presence of a cytoskeletal-like framework known as the **nuclear matrix**. Other authors dispute the presence of this structure.

Nuclear particles include the following:

A. **Interchromatin granules, clusters of irregularly distributed particles (20–25 nm in diameter) that contain ribonucleoprotein particles (RNP) and various enzymes.**

B. **Perichromatin granules are single dense granules (30–50 nm in diameter) surrounded by a less dense *halo*.** They are located at the periphery of heterochromatin and exhibit a substructure of 3 nm packed fibrils. These granules contain 4.7S RNA (and perhaps DNA) and two peptides similar to those found in heterogeneous nuclear RNPs (hnRNPs) and may represent **messenger RNPs (mRNPs).**

C. **The hnRNP particles are complexes of *precursor mRNA* (*pre-mRNA*) and proteins and are involved in processing of pre-mRNA.**

D. **Small nuclear RNPs are complexes of proteins and *small RNAs* and are involved in hnRNP splicing or in cleavage reactions.**

E. **Cajal bodies (coiled bodies), less than 2 μm in diameter, are located near, and some believe are attached to, the nucleolus.** They are thought to not only function in the formation of the enzyme telomerase but also aid in the delivery of the enzyme to telomeres of the chromosomes. Because Cajal bodies vary in number during the cell cycle, they may also function in the arrangement of nuclear structures responsible for transcription.

XIII. CHROMATIN

A. **Chromatin consists of DNA double helix complexed with *histones* and *nonhistone proteins*.** It resides within the nucleus as heterochromatin and euchromatin. The euchromatin/heterochromatin ratio is higher in malignant cells than in normal cells.
   1. **Heterochromatin** is not being transcribed and comprises approximately 90% of the total chromatin in the cell. It is formed from euchromatin that is folded into 30-nm-thick filaments.
      a. When examined under the light microscope, it appears as basophilic clumps of nucleoprotein. Although **transcriptionally inactive**, recent evidence indicates that heterochromatin functions in maintaining the integrity of chromosomal centromeres and telomeres, and, during meiosis, it also has a role in interchromosomal interactions and chromosomal segregation.
      b. One of two **X chromosomes** is transcriptionally inactive and is always condensed as heterochromatin; therefore, it is present in nearly all somatic cells of female mammals. During interphase, the inactive X chromosome, referred to as the **Barr body** (or **sex chromatin**), is visible as a dark-staining body within the nucleus.
   2. **Euchromatin**, constituting approximately 10% of the total chromatin, is **transcriptionally active** and appears in light micrographs as a lightly stained region of the nucleus. Viewed with TEM, euchromatin appears as electron-lucent regions among heterochromatin and is composed of 10-nm strings of nucleosomes.

XIV. CHROMOSOMES

A. **Chromosomes consist of chromatin extensively folded into loops that are maintained by DNA-binding proteins (Fig. 1.25).** Each chromosome contains a single, long DNA molecule and associated proteins (histones), assembled into **nucleosomes**, the structural units of chromatin packaging. Each nucleosome has a **core** of eight **histones (histone octamers)** around which the **DNA double helix** makes two spiral turns. Because the DNA double helix is extremely long, it connects an enormous number of histone octamers to each other. The DNA between adjacent histone octamers, known as **linker DNA**, appears as if it were a thin string that connects neighboring histone octamers to each other. Chromosomes are visible with the light microscope only during mitosis and meiosis, when their chromatin **condenses**; otherwise, the chromatin is **extended**.
   1. **Euchromatin** (**extended chromatin**) is formed by adjacent **nucleosomes** where the **nucleosome core** consists of two copies each of **histones H2A**, **H2B**, **H3**, and **H4**. Nucleosomes are spaced at intervals of 200 base pairs. Viewed with TEM the extended chromatin resembles beads on a string; the beads represent **nucleosomes** and the string between adjacent nucleosomes represents **linker DNA**. Nucleosomes support DNA and regulate its accessibility for replication and transcription as well as for its repair.
   2. **Heterochromatin** (**condensed chromatin**) contains an additional histone, **H1**, which wraps around groups of nucleosomes, thus forming 30-nm-diameter filaments of helical coils of six nucleosomes per turn, which is the structural unit of the chromosome.

B. **Karyotype refers to the *number* and *morphology* of *chromosomes* and is characteristic for each species.**
   1. **Haploid number** (n) is the number of a single set of unpaired chromosomes in germ cells (23 in humans).
   2. **Diploid number** (2n) is the number of two complete sets of chromosomes in somatic cells (46 in humans).

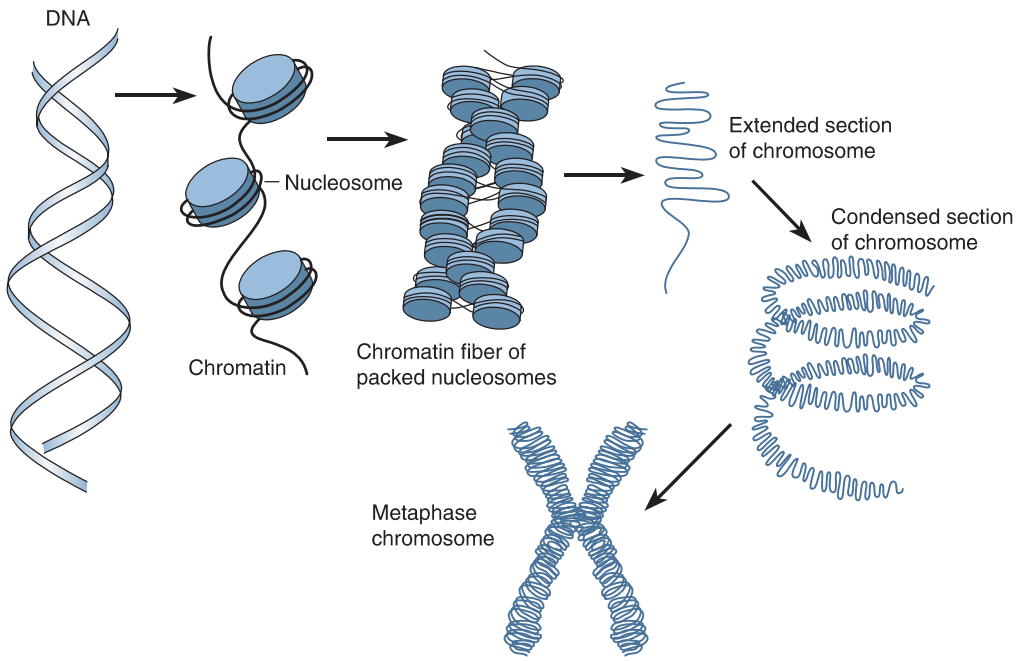


FIGURE 1.25. The packaging of chromatin into the condensed metaphase chromosome. Nucleosomes contain two copies of histones H2A, H2B, H3, and H4 in extended chromatin. An additional histone, H1, is present in condensed chromatin. DNA, deoxyribonucleic acid. (Adapted with permission from Widnell CC, Pfenninger KH. *Essential Cell Biology*. Baltimore, MD: Williams & Wilkins; 1990:47.)

C. **The total genetic complement of an individual is stored in its chromosomes.** In humans, the genome consists of 22 pairs of **autosomes** and 1 pair of **sex chromosomes** (either **XX** or **XY**), totaling 23 homologous pairs, or 46 chromosomes. Each duplicated chromosome is composed of two **chromatids** joined together at a small point, known as the **centromere**.

CLINICAL CONSIDERATIONS

As many as 100 different small molecules (e.g., methyl groups and acetyl groups), known as **epigenetic markers**, have been noted to attach to nucleotides and to histones both during embryogenesis and during adult life, as a consequence of exposure to stress and toxins. Surprisingly, these epigenetic markers may be inherited through a number of generations by changing the expressions of genes with which they are associated, even though the DNA sequence of the gene has not been altered. The investigation of these processes resulted in a new field of study known as **epigenetics**. Interestingly, acetylation of H3 histones in a specific location resulted in enhanced activity of the related gene, whereas methylation at the same location repressed gene activity.

XV. DEOXYRIBONUCLEIC ACID

DNA is a long double-stranded helical linear molecule composed of multiple nucleotide sequences. It stores the individual's genetic information and acts as a **template** for the **synthesis** of **RNA**. The complete nucleotide sequence of a human is located in the 46 chromosomes of each cell and, if stretched out and placed end-to-end, would measure almost 6 feet in length.

A. **Nucleotides are composed of a base (purine or pyrimidine), a deoxyribose sugar, and a phosphate group.**
   1. The **purines** are **adenine** (A) and **guanine** (G).
   2. The **pyrimidines** are **cytosine** (C) and **thymine** (T).

B. **The DNA double helix consists of *two complementary DNA strands* held together by hydrogen bonds between the base pairs A-T and G-C.**

C. **Exons are regions of the DNA molecule that *code* for specific RNAs.**

D. **Introns are regions of the DNA molecule, between exons, that *do not code* for RNAs.**

E. **A codon is a sequence of *three bases* in the DNA molecule that codes for a *single amino acid*.**

F. **A gene is a segment of the DNA molecule located in a specific region of a chromosome.** It is responsible not only for the coding of a single RNA molecule but also for the regulatory sequences that control the expression of a particular trait. In certain viruses, a gene may be composed of RNA rather than DNA.

G. **A genome is the complete set of hereditary information an individual possesses.** These are classified into two categories, **genes** and **noncoding segments** of the DNA (or RNA in some viruses). In fact, only about 2% of the genome is composed of genes (which code for proteins/polypeptides), whereas most of the remainder is noncoding, in that they do not code for proteins/polypeptides but possess regulatory or other functions.

CLINICAL CONSIDERATIONS

1. **Oncogenes** are the result of **mutations of certain regulatory genes**, called **proto-oncogenes**, which normally stimulate or inhibit cell proliferation and development. Genetic accidents or viruses may lead to the formation of oncogenes, which lead to unregulated cell division that may result in malignancies such as bladder cancer and myelogenous leukemia, and dominate the normal alleles (proto-oncogenes).

2. Various forms of mutational processes result in the development of distinct forms of mutations, known as **mutational signatures**. At least 20 different mutational signatures have been compiled, and some of these signatures are almost unfailingly present in exposures to particular carcinogens. Tobacco smoke is one such carcinogen (responsible for signatures 4 and 5), which was linked to the number of cigarettes smoked per day for the period of a year, known as "**pack years**." A pack year of tobacco use has been calculated to cause 150 mutations in each cell of the lungs, 97 in the larynx, 39 in the pharynx, and 18 in the bladder. **Signatures 4** and **5** include cancers of the bladder, head and neck, kidney, liver, lung, and thyroid as well as lymphoma, low-grade glioma, medulloblastoma, and melanoma.

3. Antiviral DNA vaccines are being developed against the **Zika virus** (responsible for **microcephaly** and other anomalies in human fetuses) that, instead of using attenuated viruses, insert a portion of the Zika virus DNA that codes for the viral proteins into a circular DNA known as a **plasmid**. A very large number of copies of this plasmid containing the Zika genes are injected intramuscularly with the hope that some of these modified plasmids enter the cell nucleus where mRNA is formed, which then enters the cytoplasm and is used to synthesize viral proteins. These viral proteins then assemble into virus-like particles that leave the cell and induce the immune system to form antibodies against the proteins of the Zika virus. This process is hoped to protect fetuses of pregnant mothers who are infected with the Zika virus. These DNA vaccines are very successful in mice, but, at the time of this writing, clinical studies in humans have not yet been performed.

XVI. RIBONUCLEIC ACID

RNA is a linear molecule similar to DNA; however, it is single stranded and contains **ribose** instead of **deoxyribose sugar** and **uracil** (**U**) instead of **thymine** (**T**). RNA is synthesized by **transcription** of DNA. Transcription is catalyzed by three **RNA polymerases**: I for rRNA, II for mRNA, and III for tRNA (although

the 5S rRNA is also transcribed by RNA polymerase III). Some of the noncoding segments of DNA are transcribed to form tRNA, rRNA, and regulatory RNAs. Moreover, other RNAs can act as enzymes, such as ribozymes that catalyze the formation of peptide bonds during protein synthesis.

A. mRNA carries the genetic code to the cytoplasm to direct *protein synthesis* (Fig. 1.26).

1. This single-stranded molecule consists of hundreds to thousands of nucleotides.
2. mRNA contains codons that are **complementary** to the DNA codons from which it was transcribed, including one **start codon** (**AUG**) for **initiating** protein synthesis and one of three **stop codons** (**UAA**, **UAG**, or **UGA**) for **terminating** protein synthesis.
3. mRNA is synthesized in the following series of steps:
   a. **RNA polymerase II** recognizes a **promoter** on a single strand of the DNA molecule and binds tightly to it.
   b. The DNA helix unwinds about two turns, separating the DNA strands and exposing the **codons** that act as the template for synthesis of the complementary RNA molecule.

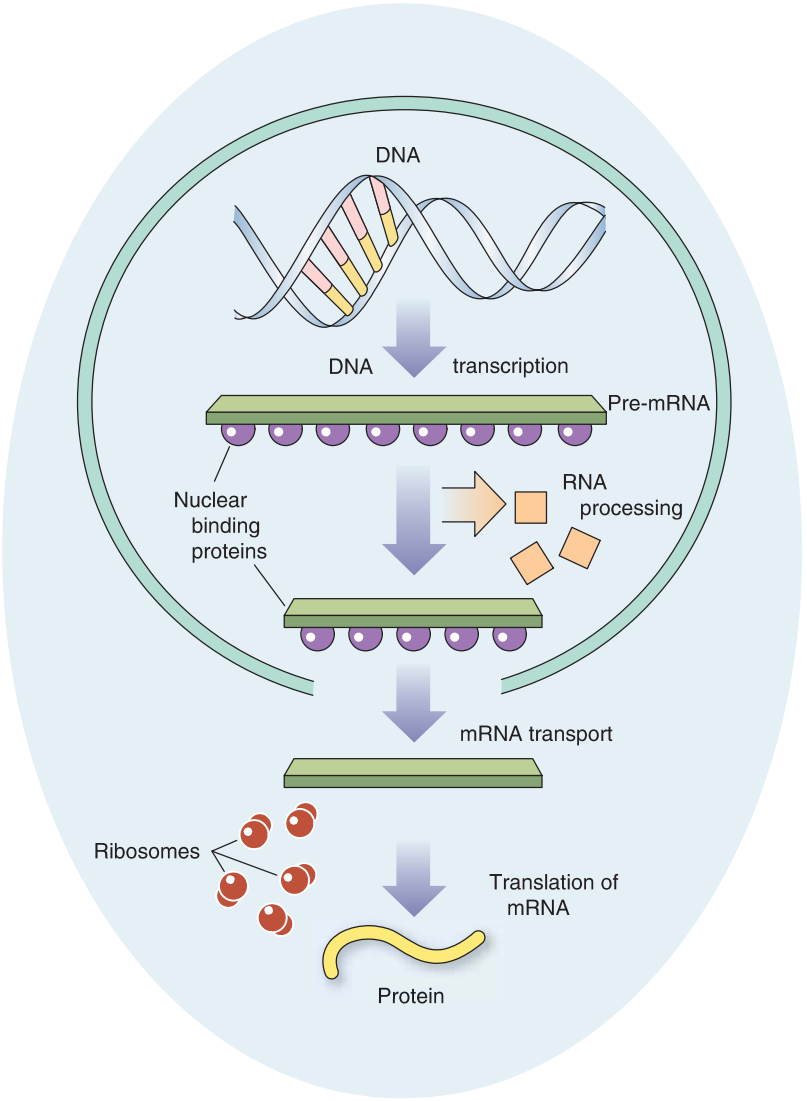


FIGURE 1.26. Steps by which genetic information encoded in deoxyribonucleic acid (DNA) is transcribed into messenger ribonucleic acid (mRNA) and ultimately converted into proteins in the cytoplasm. (Copyright from Alberts B, Bray D, Lewis J, et al. *Molecular Biology of the Cell*. 3rd ed. New York, NY: Garland Science; 1994. Adapted with permission from Garland Science/Taylor & Francis LLC.)

c. RNA polymerase II moves along the DNA strand and promotes base pairing between DNA and complementary RNA nucleotides.
d. When RNA polymerase II recognizes a **chain terminator** (stop codons—**UAA**, **UAG**, or **UGA**) on the mRNA molecule, it terminates its association with the DNA and is released to repeat transcription.
e. The primary transcript, **pre-mRNA** after the introns are removed, associates with proteins to form **hnRNP**.
f. Exons are spliced through several steps, involving **spliceosomes**, producing an **mRNP**.
g. Proteins are removed as the mRNP enters the cytoplasm, resulting in functional **mRNA**.
h. RNA segments remaining from the transcription process as introns were once thought to be degraded and recycled because they were believed to have no function. However, recent evidence shows that these RNA segments may become modified to perform regulatory functions that parallel regulatory proteins related to development, gene expression, and evolution.

B. tRNA is folded into a cloverleaf shape and contains approximately 80 nucleotides, terminating in adenylic acid (where amino acids attach).

1. Each tRNA combines with a specific amino acid that has been activated by an enzyme.
2. One end of the tRNA molecule possesses an **anticodon**, a triplet of nucleotides that recognizes the complementary codon in mRNA. If recognition occurs, the anticodon ensures that the tRNA transfers its activated amino acid molecule in the proper sequence to the growing polypeptide chain.

C. Ribosomal RNA associates with many different proteins (including enzymes) to form *ribosomes*.

1. rRNA associates with mRNA and tRNA during protein synthesis.
2. rRNA synthesis takes place in the nucleolus and is catalyzed by RNA polymerase I. A single **45S precursor rRNA** (**pre-rRNA**) is formed and **processed to form ribosomes** as follows (Fig. 1.27):
   a. Pre-rRNA associates with ribosomal proteins and is cleaved into the three sizes (28S, 18S, and 5.8S) of rRNAs present in ribosomes.

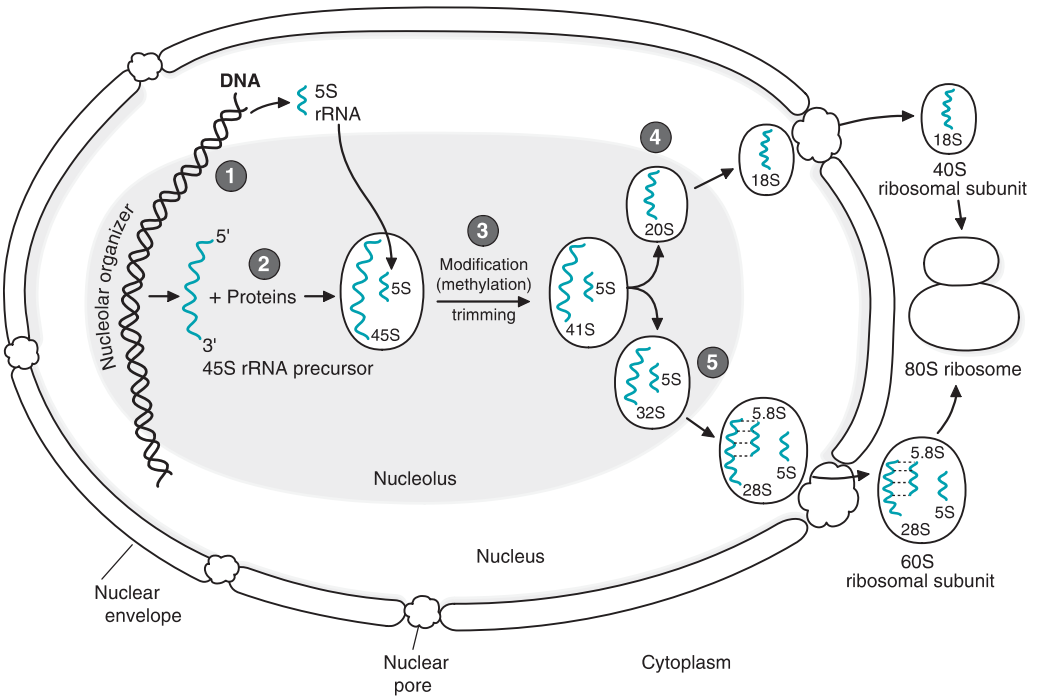


FIGURE 1.27. Formation of ribosomal ribonucleic acid (rRNA) and its processing into ribosomal subunits, which occurs in the nucleolus. DNA, deoxyribonucleic acid. (Reprinted with permission from Swanson TA, Kim SI, Glucksman MJ. *BRS Biochemistry, Molecular Biology, and Genetics*. 5th ed. Baltimore, MD: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2009:265.)

b. The **RNP** containing 28S and 5.8S rRNA then combines with 5S rRNA, (which is synthesized outside of the nucleolus via RNA polymerase III) to form the **large subunit** of the ribosome.
c. The RNP containing 18S rRNA forms the **small subunit** of the ribosome.

D. **Regulatory RNAs include microRNA (miRNA), large intergenic noncoding RNA (lincRNA), small interfering RNAs (siRNA), and Piwi-interacting RNA (piRNA).**

1. **miRNAs** first discovered in the roundworm in the 1990s, are very small segments of single-stranded RNA molecules of only 19 to 25 nucleotides in length that function to regulate gene expression. Although miRNAs are transcribed from DNA, they are noncoding and are not translated into proteins. A diverse population of more than 1,000 human miRNAs has been identified, all of which regulate developmental and physiologic processes, including proliferation, differentiation, and even apoptosis. Some miRNAs methylate specific regions of the DNA, thus preventing transcription from taking place. Other miRNAs insert into a matching portion of the mRNA strand, which prevents the translation of the mRNA; thus, the miRNA acts to regulate gene expression. miRNAs have been estimated to regulate a third or more of human genes. Because each miRNA can control hundreds of gene targets, they may influence most genetic pathways. In addition to functioning in gene expression, miRNAs also act as "central switchboards" of signaling networks that control stem cell homeostasis as well as various disease processes such as fibrosis, metastasis, and the biology of malignant cells.
2. **lincRNAs**, more than 200 nucleotides in length, also function in gene regulation. Because each cell of a female possesses two X chromosomes, one of the X chromosomes is transcribed to form lincRNAs that specifically coat that particular X chromosome and prevent the transcription of its genes. Other lincRNAs prevent the transcription of various genes on different chromosomes. Still other lincRNAs compete with certain mRNAs for miRNAs, thereby acting as decoys that protect the mRNAs from the inhibitory actions of miRNAs and facilitating the translation of the mRNA to synthesize a particular protein.
3. **siRNAs**, also known as **silencing RNAs**, are similar to miRNAs; they are 19 to 25 nucleotides in length, but they frequently arise from the genome of RNA viruses that infect a cell (although some siRNAs are transcribed from the cell's own genome). They resemble miRNAs in their mode of action in that they also methylate specific regions of the DNA and thus interfere with the process of transcription.
4. **piRNA** is a small RNA, about 25 to 30 nucleotides long, which combines with piwi protein. The piRNA–piwi protein complex is believed to be responsible for the process of placing epigenetic marks on the chromosomes.

CLINICAL CONSIDERATIONS

miRNAs have been shown to repress certain cancer-related genes. Additionally miRNAs are known to depress angiogenesis, which may become useful in clinically restricting cancer growth. Thus, miRNAs may prove useful in the diagnosis and treatment of cancer. Certain other miRNAs have been shown to regulate differentiation (e.g., repressing adipocyte formation, an understanding that may lead to a clinical treatment modality for obesity). Still other miRNAs repress certain cancer-related genes, such as in lung cancer, where human lung cancer cells treated with miRNAs had a reduced rate of proliferation and diminished capability to migrate, thus reducing their invasive abilities. Additionally, the treated cells had a greater rate of apoptosis, reinforcing the hope that miRNAs may prove useful in the diagnosis and treatment of cancer. Moreover, other miRNAs have been shown to function in cardiac physiology and pathology, such as in the remodeling of the ventricles; apoptosis; and hypertrophy of cardiac myocytes, myocardial infarcts, and fibrosis subsequent to the death of cardiac muscle cells.

XVII. CELL CYCLE

A. **The cell cycle (Fig. 1.28) varies in length in different types of cells but is repeated each time a cell divides.** It is composed of not only the series of events that prepare the cell to divide into two daughter cells but the process of cell division as well.

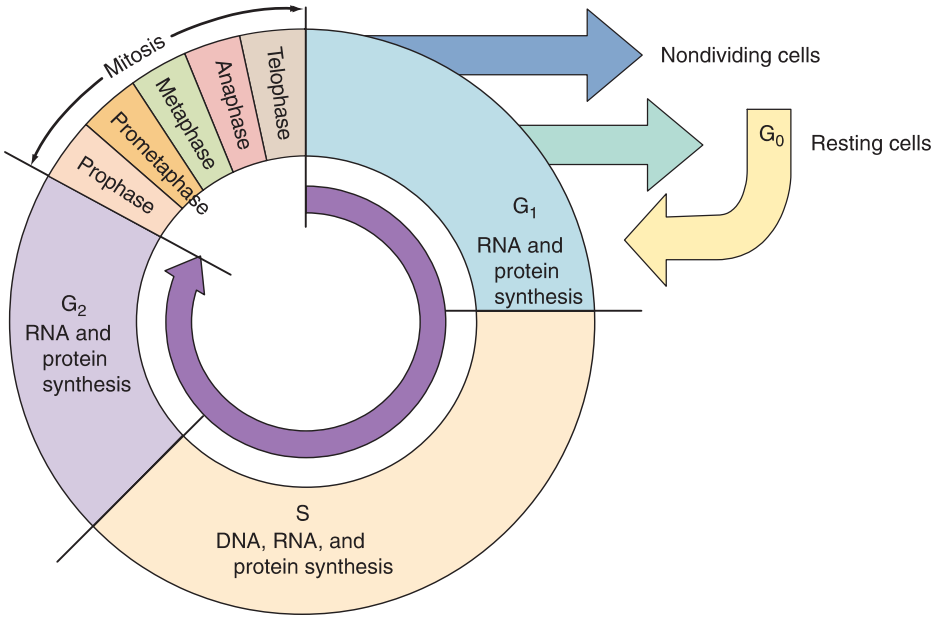


FIGURE 1.28. Stages of the cell cycle in dividing cells. Differentiated cells that no longer divide have left the cycle, whereas resting cells in the G_0 state may reenter the cycle and begin dividing again. DNA, deoxyribonucleic acid; RNA, ribonucleic acid. (Adapted with permission from Widnell CC, Pfenninger KH. *Essential Cell Biology*. Baltimore, MD: Williams & Wilkins; 1990:58.)

1. The cell cycle is **temporarily suspended** in nondividing resting cells (e.g., peripheral lymphocytes), which are in the **gap outside phase** (**G_0 phase**). Such cells may reenter the cycle and begin to divide again. However, it is **permanently interrupted** in differentiated cells that do not divide (e.g., most cardiac muscle cells and neurons).

B. Two major periods comprise the cell cycle: *interphase* (interval between cell divisions) and *M phase* (*mitosis*, the period of cell division).

1. **Interphase** is considerably longer than the M phase and is the period during which **the cell doubles in size and DNA content**. It is divided into three separate phases (**G_1**, **S**, and **G_2**), during which specific cellular functions occur.
   - **a. G_1 phase** (**gap one phase**) lasts for hours to several days.
     - **(1)** Occurring after mitosis, it is the period during which the cell grows and proteins are synthesized, restoring the daughter cells to normal volume and size.
     - **(2)** Trigger proteins are synthesized that enable the cell to reach a threshold (**restriction point**) and proceed to the S phase. Cells that fail to reach the restriction point become resting cells and enter the **G_0 phase**, where they remain for a period of time (days, months, or years), to eventually reenter the cell cycle or remain in the G_0 phase permanently.
   - **b. S phase** (**synthetic phase**) lasts 8 to 12 hours in most cells.
     - **(1)** DNA is replicated and histone and nonhistone proteins are synthesized, resulting in **duplication of the chromosomes**. The **centrosomes** are also duplicated.
   - **c. G_2 phase** (**gap two phase**) lasts 2 to 4 hours.
     - **(1)** This phase extends to the process of mitosis. **Centrioles** duplicate, each forming a new daughter centriole; the energy required for the completion of mitosis is accumulated; and RNA and proteins, including tubulin for the spindle apparatus, are synthesized.
2. A category of proteins known as **cyclins**, as well as **cyclin-dependent kinases** (**CDKs**), initiate and/or induce the cell's progression through the cell cycle. The progression can be stopped at various **checkpoints** at each of which the accuracy of the cellular events is monitored.
   - **a.** During the G_1 phase, **cyclins D and E** bind to their respective CDKs, enabling the cell to enter and advance through the **S phase**. During both the G_1 phase and the S phase the replication of DNA is monitored, and, if errors are detected, the cell cycle cannot continue until the errors are corrected. These are known as the **G_1 DNA damage checkpoint** and the **S DNA damage checkpoint**, respectively.

b. **Cyclin A** binds to its CDKs, thus enabling the cell to leave the **S phase** and enter the **G_2 phase** as well as to manufacture **cyclin B**. Two additional DNA checkpoints in the G_2 phase are the **unreplicated DNA checkpoint**, which cannot be passed unless all of the DNA was replicated in the S phase, and the **G_2 damage checkpoint** that prevents the continuation of the G_2 phase if errors are present in the replicated DNA.

c. Cyclin B binds to its CDK, inducing the cell to leave the **G_2 phase** and enter the **M phase**. In the beginning of the M phase, the spindle apparatus is monitored; if the spindle assembly is faulty, the cell cannot leave the M phase. This is referred to as the **spindle assembly checkpoint**. Near the termination of the M phase, the condition of the chromosomes is monitored, and, if any of the chromosomes are "sticking" to each other, the cell is not permitted to leave the M phase. This is referred to as the **chromosome segregation checkpoint**.

C. Mitosis (Fig. 1.29; Table 1.8) lasts 1 to 3 hours. It follows the G_2 phase and completes the cell cycle. It includes segregation of the replicated chromosomes, division of the nucleus (**karyokinesis**), and

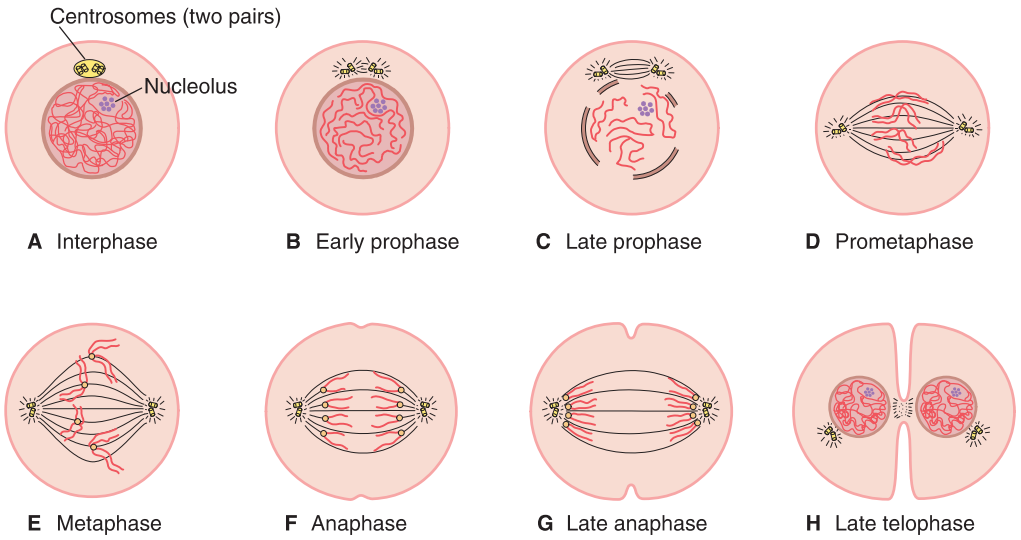


FIGURE 1.29. Events in various phases of mitosis. (Redrawn with permission from Kelly DE, Wood RL, Enders AC. *Bailey's Textbook of Microscopic Anatomy*. 18th ed. Baltimore, MD: Williams & Wilkins; 1984:89.)

table **1.8** Stages of Mitosis

Stage	DNA Content	Identifying Characteristics
Prophase (early)	DNA content doubles in the S phase of interphase (4n); also, centrioles replicate	Nuclear envelope and nucleolus begin to disappear. Chromosomes condense; they consist of two sister chromatids attached at the centromere.
Prophase (late)		Centrioles migrate to opposite poles and give rise to spindle fibers and astral rays.
Prometaphase	Double complement of DNA (4n)	Nuclear envelope disappears. Kinetochores develop at centromeres, and kinetochore microtubules form.
Metaphase	Double complement of DNA (4n)	Maximally condensed chromosomes align at the equatorial plate of the mitotic spindle.
Anaphase	Double complement of DNA (4n)	Daughter chromatids separate at centromere.
Anaphase (late)		Each chromatid migrates to an opposite pole of the cell along the microtubule (karyokinesis). A cleavage furrow begins to form.
Telophase	Each new daughter cell contains a single complement of DNA (2n)	The furrow (midbody) now deepens between the newly formed daughter cells (cytokinesis). Nuclear envelope reforms, nucleoli reappear, chromosomes disperse forming new interphase nucleus.

finally division of the cytoplasm (**cytokinesis**), resulting in the production of two **identical** daughter cells. Mitosis consists of five major stages (phases).

1. **Prophase** begins when the duplicated chromosomes condense and become visible. Each chromosome is composed of two **sister chromatids** (future **daughter chromosome**) attached to each other at the **centromere**. A number of proteins assemble on each chromatid in the vicinity of the centromere forming a **kinetochore** on the opposing aspects of each chromatid (thus there will be two kinetochores, one on each chromatid, facing opposite poles of the cell). During prophase, the nucleolus and nuclear envelope begin to dissipate.
   - **a.** The **centrosome** contains **centrioles** and a pericentriolar cloud of material containing **γ-tubulin rings**. It is the principal **MTOC** of the cell.
   - **b.** As centrosomes migrate to opposite poles of the cell, they set up two MTOCs, one at each pole of the dividing cell, and each MTOC gives rise to three sets of microtubules that comprise the **spindle apparatus** of the cell.
     - **(1) Astral microtubules** arise from the MTOCs in a spoke-like fashion and ensure that the MTOCs maintain their correct location at the opposite poles of the cell near the cell membrane. In this fashion, astral microtubules facilitate the proper orientation of the spindle apparatus.
     - **(2) Polar microtubules** arise from each MTOC, grow toward each other, and meet near the equator of the cell. They function in ensuring that the two MTOCs are kept apart from each other and maintain their respective locations.
     - **(3) Kinetochore microtubules** emanate from each MTOC and grow toward the chromosomes. Once they reach each chromosome, they attach to the kinetochores of the sister chromatids and, during anaphase, begin the process of dragging sister chromatids to opposing poles of the cell.
2. **Prometaphase** begins when the nuclear envelope disappears, allowing the chromosomes to disperse apparently randomly in the cytoplasm. Sister chromatids are held together by **cohesions**, a group of binding proteins, and their compressed condition is maintained by the proteins **condensin**.
3. **Metaphase** is the phase during which the duplicated condensed chromosomes align at the equatorial plate of the mitotic spindle and become attached to kinetochore microtubules at their kinetochore. If this connection is not stable, **anaphase-promoting complex** interferes with cyclin E, and the cell cannot progress through metaphase.
4. **Anaphase** begins as sister chromatids separate at the centromere and daughter chromosomes move to opposite poles of the cell.
   - **a.** The spindle shortens.
   - **b.** In the later stages of anaphase, a **cleavage furrow** begins to form around the cell as the **contractile ring**, a band of actin filaments, contracts.
5. **Telophase** is characterized by each set of chromosomes reaching the pole, a deepening of the cleavage furrow; the **midbody** (containing overlapping polar microtubules) is now between the newly forming daughter cells.
   - **a.** Microtubules in the midbody are depolymerized, facilitating **cytokinesis** and formation of two identical daughter cells.
   - **b.** The **nuclear envelope** is reestablished around the condensed chromosomes in the daughter cells, and **nucleoli reappear**. Nucleoli arise from the specific **nucleolar-organizing regions** (called **secondary constriction sites**), which are carried on five separate chromosomes in humans (see Section XI Nucleolus).
   - **c.** The daughter nuclei gradually enlarge, and the condensed chromosomes disperse to form the typical interphase nucleus with heterochromatin and euchromatin.
   - **d.** At the end of cytokinesis, the mother centriole of the duplicated pair apparently moves from the newly forming nuclear pole to the intercellular bridge. This event is necessary to initiate disassembly of the midbody microtubules and complete the separation of the daughter cells. If this event fails, DNA replication is arrested at one of the G_1 checkpoints during the next interphase.

CLINICAL CONSIDERATIONS

Transformed cells have lost their ability to respond to regulatory signals controlling the cell cycle and may therefore undergo cell division, indefinitely, thus becoming cancerous. **Vinca alkaloids** may arrest these cells in mitosis, whereas drugs that block purine and pyrimidine synthesis may arrest these cells in the S phase of the cell cycle.

XVIII. MEIOSIS

A. Meiosis (Fig. 1.30) is a special form of cell division in germ cells (oogonia and spermatogonia) in which the *chromosome number* is reduced from *diploid chromosome set* (*2n*) to *haploid* (*n*). These events are accomplished via two reduction divisions.

1. This occurs in developing germ cells in preparation for sexual reproduction. Subsequent fertilization results in **diploid zygotes**.
2. DNA content of the original diploid cell is double the number of DNA copies (4n) in the S phase preparatory to meiosis.
   - **a.** This phase is followed by two successive cell divisions that give rise to **four haploid cells**.
   - **b.** In addition, **recombination** of maternal and paternal genes occurs by **crossing over** and **random assortment**, yielding the unique haploid genome of the gamete.

B. The stages of meiosis are meiosis I (reductional division) and meiosis II (equatorial division).

1. **Reductional division** (**meiosis I**) occurs after interphase during the cell cycle, when the DNA content is duplicated, whereas the chromosome number (46) remains unchanged, giving the cell a **4CDNA content** (considered to be the total DNA content of the cell).
   - **a. Prophase I** is divided into five stages (leptotene, zygotene, pachytene, diplotene, and diakinesis), which accomplish the following events:
     - **(1)** Chromatin condenses into the visible chromosomes, each containing two chromatids joined at the centromere.

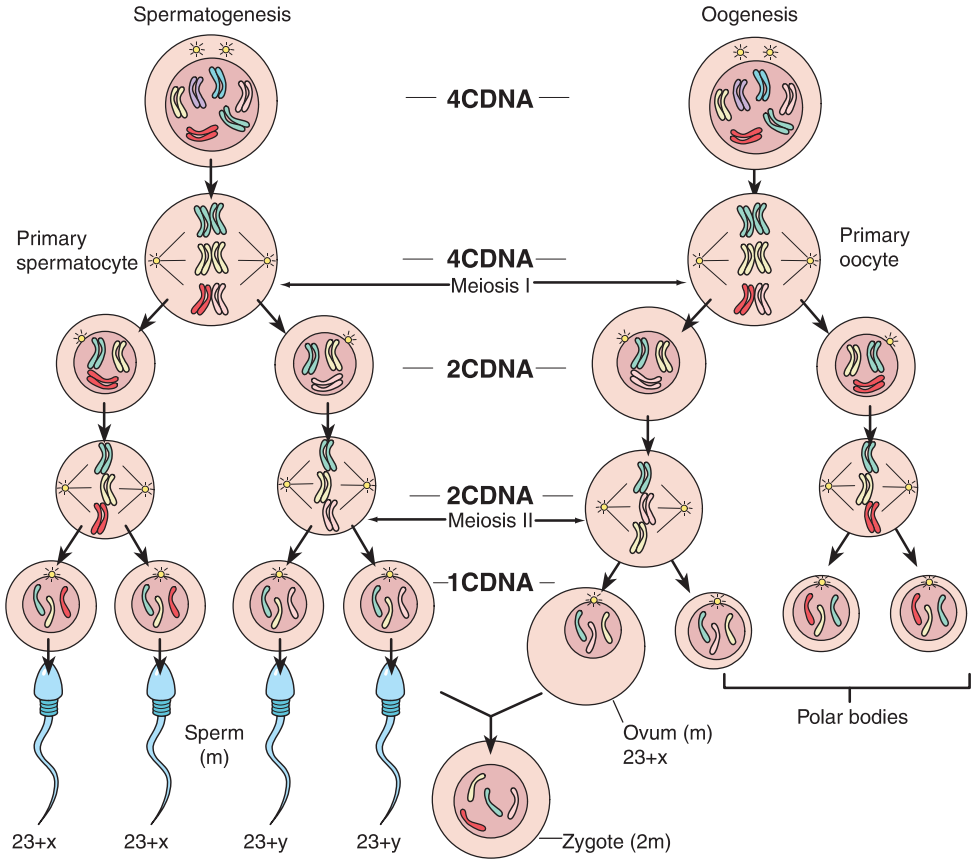


FIGURE 1.30. Meiosis in men and women. Spermatogenesis in the male gives rise to sperm, each containing the haploid number of chromosomes. Oogenesis in the female gives rise to an ovum with the haploid number of chromosomes. Fertilization reconstitutes the diploid number of chromosomes in the resulting zygote. (Adapted with permission from Widnell CC, Pfenninger KH. *Essential Cell Biology*. Baltimore, MD: Williams & Wilkins; 1990:69.)

(2) Homologous maternal and paternal chromosomes pair via the **synaptonemal complex**, forming a **tetrad**. **Crossing over** (random exchanging of genes between segments of homologous chromosomes) occurs at the **chiasmata**, thus **increasing genetic diversity**.
(3) The nucleolus and nuclear envelope disappear.

b. **Metaphase I**
(1) Homologous pairs of chromosomes align on the equatorial plate of the spindle in a random arrangement, facilitating genetic mixing.
(2) Spindle fibers from either pole attach to the **kinetochore** of any one of the chromosome pairs, thus ensuring genetic mixing.

c. **Anaphase I**
(1) This phase is similar to anaphase in mitosis, except, in mitosis, the two chromatids are pulled apart and each is delivered to each pole of the cell, whereas in anaphase I of meiosis the homologous chromosomes are separated in such a fashion that **two chromatids** remain held together as they are being pulled to each pole of the cell.
(2) Chromosomes migrate to the poles.

d. **Telophase** I is similar to telophase in mitosis in that the nuclear envelope is reestablished and two daughter cells are formed via cytokinesis.
(1) Each daughter cell now contains 23 chromosomes (n) but has a **2CDNA content**.
(2) Each chromosome is composed of **two** similar **sister chromatids** (but not genetically identical following recombination).

2. **Equatorial division** (**meiosis II**) begins soon after the completion of meiosis I, following a brief interphase **without DNA replication** (**no S phase**).
a. The chromosomes separate and the two daughter cells divide, resulting in the distribution of chromosomes into four daughter cells, each containing its own **unique recombined genetic material** (**1CDNA**; **n**). Thus, every gamete contains its own unique set of genetic materials.
b. The stages of meiosis II are similar to those of mitosis; thus, the stages are named similarly (prophase II, metaphase II, anaphase II, and telophase II).
c. Meiosis II occurs more rapidly than mitosis.

CLINICAL CONSIDERATIONS

Chromosome nondisjunction

During prophase I of meiosis I, chromosome pairs align themselves at the equatorial plate and exchange genetic materials. During anaphase I (as well as anaphase II), the chromosome pairs will separate and begin their migrations to opposite poles. Sometimes the members of a pair fail to separate, resulting in one daughter cell containing an extra chromosome ($n + 1 = 24$), whereas the daughter cell at the opposite pole is minus a chromosome ($n - 1 = 22$). This development is known as **nondisjunction**. Upon fertilization with a normal gamete containing 23 chromosomes, the resulting zygote will contain either 47 chromosomes (trisomy for that extra chromosome) or 45 chromosomes (monosomy for that missing chromosome). Chromosomes 8, 9, 13, 18, and 21 are those chromosomes most frequently affected by nondisjunction.

Aneuploidy, defined as an abnormal number of chromosomes, can be detected by karyotyping.

1. **Down syndrome** (**trisomy 21**) is characterized by intellectual disability, short stature, stubby appendages, congenital heart malformations, and other defects.
2. **Klinefelter syndrome** (**XXY**) is aneuploidy of the sex chromosomes, characterized by infertility; variable degrees of masculinization; and feminization including the presence of small testes, gynecomastia, and widened hips.
3. **Turner syndrome** (**XO**) is **monosomy** (a form of aneuploidy) of the sex chromosomes, characterized by short stature, webbed neck, sterility, and various other abnormalities. This is the only monosomy compatible with life, and mental development is normal.

XIX. APOPTOSIS AND NECROSIS

A. Apoptosis is programmed cell death, whereby cells are removed from tissues in an orderly fashion as a part of normal maintenance or during development.

1. Cells that undergo programmed cell death have several **morphologic features**.
   a. They include chromatin condensation (known as pyknosis), breaking up of the nucleus (karyorrhexis), and "blebbing" of the cell membrane.
   b. The cell shrinks and is fragmented into membrane-enclosed fragments called **apoptotic bodies**.
2. Apoptotic cells do not pose a threat to surrounding cells, because changes in their cell membranes make them subject to rapid phagocytosis by macrophages and by neighboring cells. Macrophages that phagocytose apoptotic cells do not release cytokines that initiate the inflammatory response.
3. The signals that induce apoptosis may occur through several mechanisms.
   a. Genes that code for enzymes, called **caspases**, play an important role in the process.
   b. Certain cytokines, such as **tumor necrosis factor**, may also activate caspases that degrade regulatory and structural proteins in the nucleus and cytoplasm, leading to the morphologic changes characteristic of apoptosis.
4. Cells may protect themselves from apoptosis by producing survival factors, including proteins known as **inhibitors of apoptosis**. These proteins can bond with activated caspases, thus inhibiting them from performing their functions.

CLINICAL CONSIDERATIONS

Defects in the process of programmed cell death contribute to many major diseases. Excessive apoptosis causes extensive nerve cell loss in Alzheimer disease and stroke, whereas insufficient apoptosis has been linked to cancer and other autoimmune diseases.

B. Necrosis is also a form of cell death, but death does not occur in a regulated fashion as in apoptosis, instead the cell succumbs to one or more traumatic events. When a cell undergoes necrosis, it usually ruptures, its contents are released into the extracellular space, and the body initiates an inflammatory response. Necrosis can cause serious problems for the individual, and, if it is widespread, it may result in death.

Review Test

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A herpetologist is bitten by a poisonous snake and is taken to the emergency department with progressive muscle paralysis. The venom is probably incapacitating his

(A) Na^+ channels.
(B) Ca^{2+} channels.
(C) phospholipids.
(D) acetylcholine receptors.
(E) spectrin.

2. Examination of the blood smear of a young patient reveals misshapen red blood cells, and the pathology report indicates hereditary spherocytosis. Defects in which one of the following proteins cause this condition?

(A) Signaling molecules
(B) G proteins
(C) Spectrin
(D) Hemoglobin
(E) Catalase

3. A baby was brought into the hospital unconscious and died shortly after being admitted. Because of the presence of contusions and other signs of child abuse, an autopsy confirmed that the baby had diffuse axonal injury. Examination of the affected tissue displays irreparable cleavage of a specific protein, with an ensuing destruction of the neuronal cytoskeleton leading to loss of cell membrane integrity and eventual cell death. The cleaved protein is known as

(A) ankyrin.
(B) spectrin.
(C) integrin.
(D) vinculin.
(E) band 4.1.

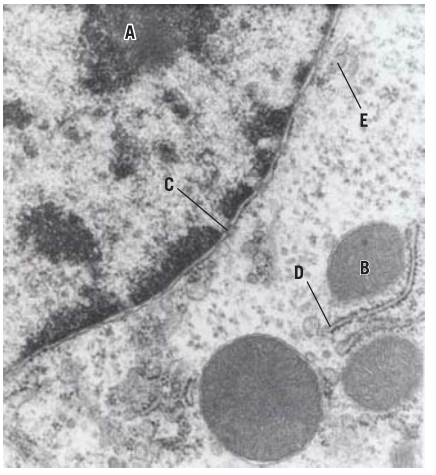
4. A 30-year-old man with very high blood cholesterol levels (290 mg/dL) has been diagnosed with premature atherosclerosis. His father died of a heart attack at age 45, and his mother, aged 44, has coronary artery disease. Which of the following is the most likely explanation of his condition?

(A) He has a lysosomal storage disease and cannot digest cholesterol.
(B) He has a peroxisomal disorder and produces low levels of hydrogen peroxide.
(C) The SER in his hepatocytes has proliferated and produced excessive amounts of cholesterol.
(D) He has a genetic disorder and synthesizes defective LDL receptors.
(E) He is unable to manufacture endosomes.

5. A tissue section from a tumor has been immunochemically stained for the intermediate filament protein glial fibrillary acidic protein (GFAP). Based on the reddish brown staining observed the tumor has originated from which of the following?

(A) Oligodendrocytes
(B) Chondrocytes
(C) Neurons
(D) Endothelial cells
(E) Fibroblasts

6. This question is based on the electron micrograph and the patient scenario below:



A 42-year-old male patient is diagnosed with Huntington disease, a condition that is due to a mutated form of the HTT protein. Which of the labeled structures in this electron micrograph is responsible for the interference of the normal functioning of the cell?

(A) A
(B) B
(C) C
(D) D
(E) E

7. A male child at puberty is determined to have Klinefelter syndrome. Although the parents have been informed of the clinical significance, they have asked for an explanation of what happened. Identify the item that should be discussed with the parents.

(A) Trisomy of chromosome 21
(B) Loss of an autosome during mitosis
(C) Loss of the Y chromosome during meiosis
(D) Nondisjunction of the X chromosome
(E) Loss of the X chromosome

The following two questions are based on this scenario:

A female baby is diagnosed with Leigh disease, a lethal condition.

8. Leigh disease has been demonstrated to be related to defects in which of the following organelles?

(A) Lysosomes
(B) Peroxisomes
(C) Mitochondria
(D) RER
(E) TGN

9. What is the cause of Leigh disease?

(A) Accumulation of lysosomal degradation products
(B) Overproduction of catalase
(C) Uncoupling of phosphorylation from oxidation
(D) Mutations in the DNA
(E) Lack of ribophorin

10. Which is true concerning Turner syndrome?

(A) It is caused by trisomy.
(B) It is caused by aneuploidy.
(C) It affects only males.
(D) It affects both males and females.
(E) It is due to incomplete mitosis.

Answers and Explanations

1. **D.** Snake venom usually blocks acetylcholine receptors, preventing depolarization of the muscle cell. The Na^+ and Ca^{2+} channels are not incapacitated by snake venoms.
2. **C.** Hereditary spherocytosis is caused by a defect in spectrin, ankyrin, band 3 protein, or protein 4.2 that renders the interactions among these proteins defective, thus destabilizing the spectrin–actin complex of the cytoskeleton. Although defects in hemoglobin (the respiratory protein of erythrocytes) also cause red blood cell anomalies, hereditary spherocytosis is not one of them.
3. **B.** Spectrin. Diffuse axonal injury in babies is usually due to shearing damage to the axons—especially at the interface of white matter and gray matter. This results in an irreparable cleavage of spectrin, with an ensuing destruction of the neuronal cytoskeleton leading to loss of cell membrane integrity and eventual cell death. The patient becomes comatose and 90% of the time never recovers. Although ankyrin, integrin, vinculin, and band 4.1 are all associated with the cytoskeleton and cell membrane, they are not involved in diffuse axonal injury in babies.
4. **D.** Cells import cholesterol by the receptor-mediated uptake of LDLs in coated vesicles. Certain individuals inherit defective genes and cannot make LDL receptors, or they make defective receptors that cannot bind to clathrin-coated pits. The result is an inability to internalize LDLs, which leads to high levels of LDLs in the bloodstream. High LDL levels predispose a person to premature atherosclerosis and increase the risk of heart attacks.
5. **A.** The intermediate filament protein GFAP is present in glial cells, including microglia, oligodendrocytes, fibrous astrocytes, and Schwann cells. Vimentin is found in cells of connective tissue origin, which include fibroblasts, chondrocytes, and endothelial cells. Neurons contain intermediate neurofilaments, which would not stain for either GFAP or vimentin.
6. **C.** Certain neurons have been shown to accumulate mutated Huntingtin proteins (coded by the mutated HTT genes) in their nuclei. The mutation affects nucleoporins that cause functional disturbances in the NPCs, which become unable to permit the transport of proteins from the nucleus into the cytoplasm. The accumulated proteins in the nucleus interfere with the functions of the neuron, resulting in this debilitating, lethal condition.
7. **D.** Klinefelter syndrome occurs only in men. This condition results from nondisjunction of the X chromosome during meiosis, resulting in an extra X chromosome in somatic cells. These cells therefore have a normal complement of autosomal chromosomes (22 pairs) and have an extra X chromosome instead of one pair of sex chromosomes (XY). These individuals have an XXY genotype, resulting in 47 total chromosomes rather than the normal complement of 46. This syndrome is an example of trisomy of the sex chromosomes. Down syndrome is an example of an autosomal trisomy, specifically trisomy of chromosome number 21. Both syndromes have profound complications.
8. **C.** Leigh disease is a mitochondrial disease. Cells that have high energy requirements are especially vulnerable in this condition because the disease targets the enzymes responsible for oxidative phosphorylation, preventing the formation of a requisite amount of ATP.
9. **D.** Leigh disease is due to mutations either in the mitochondrial DNA itself or to mutations in the nuclear DNA that codes for mitochondrial proteins.
10. **B.** Turner syndrome patients are females with an abnormal chromosome count (aneuploidy). Instead of 46 chromosomes (22 pairs of autosomes and 2 allosomes; either XX or XY), the cells of these individuals possess 45 chromosomes, the normal number of autosomes, but only a single X chromosome (the other sex chromosome is missing due to nondisjunction during gametogenesis). Therefore, Turner syndrome, a monosomy, is also known as 45,X (also 45,X0). This is the only monosomy of the sex chromosomes compatible with life, and mental development is normal, but these patients have a number of medical complications, including diabetes and cardiovascular problems, which probably account for their shorter life spans.

chapter 2

Extracellular Matrix

I. OVERVIEW—EXTRACELLULAR MATRIX

A. Structure. Although the **extracellular matrix (ECM)**, an organized meshwork of **macromolecules** surrounding and underlying cells, varies in composition, it generally consists of an amorphous **ground substance** (containing primarily glycosaminoglycans [GAGs], proteoglycans, and glycoproteins) and **fibers** (Fig. 2.1).

B. Functions. The **extracellular environment** consists of the ECM as well as the **extracellular fluid (ECF)** in which ions and small molecules are dissolved. By affecting the metabolic activities of cells that contact it, the ECM may alter and influence the shape, migration, mitotic activity, and differentiation of those cells as well as their interaction with other cells. Additionally, the ECM provides physical support against compressive as well as tensile forces.

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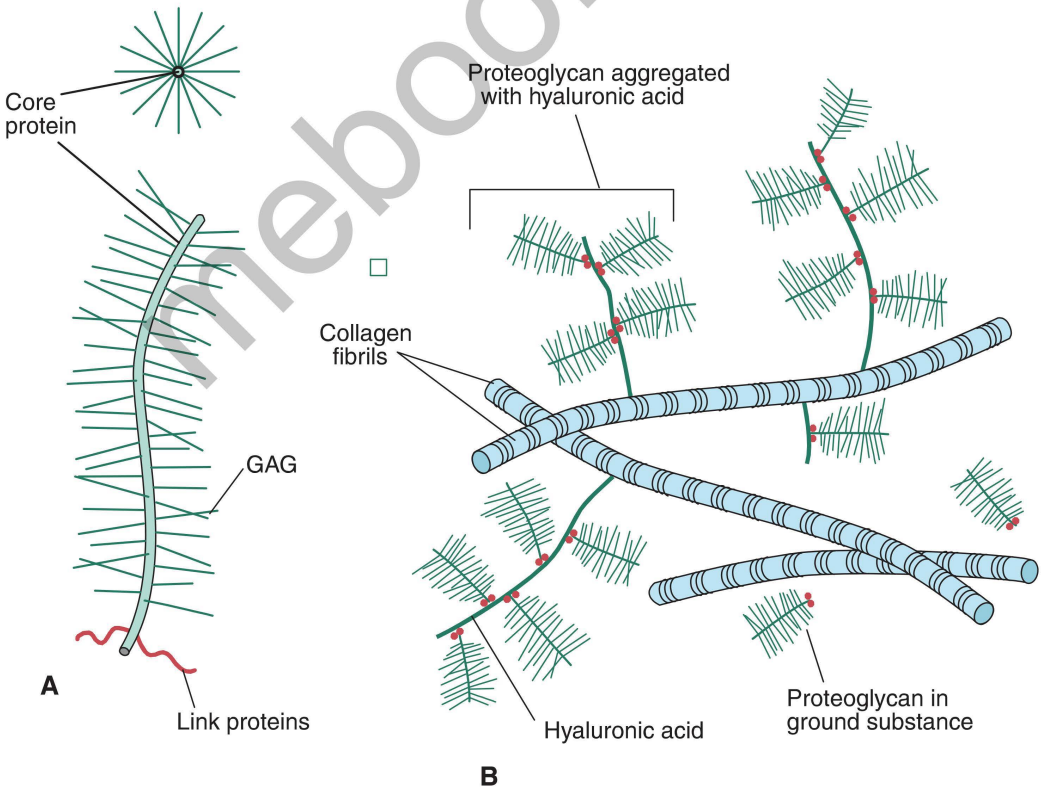


FIGURE 2.1. Components of the extracellular matrix (ECM). **A.** Proteoglycan molecule, two views. **B.** Relationships among various ECM molecules. GAG, glycosaminoglycan. (Adapted with permission from Henrikson RC, Kaye GI, Mazurkiewicz JE. NMS Histology. Baltimore, MD: Lippincott Williams & Wilkins; 1997:104.)

II. GROUND SUBSTANCE

A. GAGs are long, unbranched polysaccharides composed of repeating identical *disaccharide units*.

1. An **amino sugar**, either *N*-acetylglucosamine or *N*-acetylgalactosamine, is always one of the repeating disaccharides. Because GAGs are commonly **sulfated** and usually possess a **uronic acid sugar**, they have a strong **negative charge**.
2. GAGs may be classified into four main groups on the basis of their chemical structure (Table 2.1).
   a. **Hyaluronic acid** (**hyaluronan**), a very large unsulfated molecule (up to 20 μm in length and a molecular mass as much as 10,000 kDa), is not attached to a core protein.
   b. The other three GAG groups are **chondroitin sulfate** and **dermatan sulfate**, **heparin** and **heparan sulfate**, and **keratan sulfate**.

CLINICAL CONSIDERATIONS

Taking the popular dietary supplement **chondroitin sulfate** and/or **glucosamine** has been reported to reduce the risk of osteoarthritis, joint degeneration, and cartilage deterioration. Patients with knee osteoarthritis experienced significantly less pain and increased function while taking these compounds when compared with patients on placebo, but radiographic evidence from examining knee joint degeneration was complicated by the fact that the placebo group had a smaller loss of cartilage than had been anticipated, so no definite conclusions could be reached concerning the efficacy of these supplements.

B. Proteoglycans consist of a *core protein* to which numerous GAGs are attached. These large molecules are shaped like a bottlebrush (Fig. 2.1A).

1. Their core proteins, molecular size, and the number and types of GAGs they contain show marked heterogeneity in proteoglycans, which frequently act as binding sites for **signaling molecules**.
2. Proteoglycans may attach to hyaluronic acid via their core proteins to form large complex aggregates (e.g., aggrecan proteoglycan aggregate of cartilage).
3. Because GAGs are negatively charged, they attract osmotically active cations (e.g., Na^+). The positive charge conferred by sodium ions attracts waters of hydration resulting in a heavily hydrated matrix that strongly **resists compression**. These huge molecules have a large domain and prevent the rapid infiltration of fluids through the connective tissue as is evident when observing how slowly a bleb of subcutaneous injection is absorbed.

C. Glycoproteins (multiadhesive glycoproteins) are multifunctional molecules whose domains bind to ECM components and to receptors on the cell surface, thereby promoting adhesion between the cell and the matrix (Table 2.2).

1. **Fibronectin**
   a. The three types of fibronectin are matrix fibronectin, which forms fibrils in the ECM; cell surface fibronectin, a protein that transiently attaches to the surface of cells; and plasma fibronectin, a circulating plasma protein that functions in blood clotting, wound healing, and phagocytosis.

table 2.1 Glycosaminoglycan Classification

Group	Glycosaminoglycan	Linked to Core Protein	Sulfated	Major Locations in Body
I	Hyaluronic acid	No	No	Synovial fluid, vitreous humor, cartilage, skin, most connective tissues
II	Chondroitin sulfate Dermatan sulfate	Yes Yes	Yes Yes	Cornea, cartilage, bone, adventitia of arteries Skin, blood vessels, heart valves
III	Heparin Heparan sulfate	Yes Yes	Yes Yes	Lung, skin, liver, mast cells Basal laminae, lung, arteries, cell surfaces
IV	Keratan sulfate	Yes	Yes	Cornea, cartilage, nucleus pulposus of intervertebral disks

table 2.2 Major ECM Glycoproteins

Glycoprotein	Location	Function
Fibronectin	Most connective tissues	Binds collagen, heparan sulfate, various cell surface receptors, and CAMs, thus mediating cell adhesion to the ECM
Laminin	Basal laminae of epithelial cells and external laminae of muscle cells and Schwann cells	Anchors cells to their basal laminae (and external lamina), thus assisting in adhering epithelial cells to the underlying connective tissue
Entactin	Basal laminae of epithelial cells and external laminae of muscle cells and Schwann cells	Links laminin to type IV collagen of the basal laminae (and external laminae)
Tenascin	Embryonic connective tissue	Facilitates cell–matrix adhesion, thus assisting in cell migration
Chondronectin	Cartilage	Assists cartilage cells in adhering to their matrix
Osteonectin	Bone	Assists bone cells in adhering to their matrix Influences calcification of the bone matrix

CAM, cell adhesion molecule; ECM, extracellular matrix.

b. **Matrix fibronectin** has domains for **binding collagen**, **heparin**, various **cell surface receptors**, and **cell adhesion molecules** (**CAMs**). It **mediates cell adhesion** to the ECM by binding to fibronectin receptors on the cell surface.

CLINICAL CONSIDERATIONS

Wound healing in adults involves the formation of **fibronectin tracks** along which cells migrate to their destinations. In **connective tissue**, wound healing is often characterized by migration of fibroblasts across blood clots, where they adhere to fibronectin. In **epithelia**, wound healing involves reepithelialization, which depends on the **basal lamina serving as a scaffold** for cell migration to cover the denuded area; epithelial cell proliferation and replacement then occur.

2. **Laminin** is a large cross-shaped molecule located in the basal laminae, where it is synthesized by adjacent epithelial cells; in external laminae of muscle cells and Schwann cells, it is synthesized by those respective cells.
   a. The arms of the laminin molecule have binding sites for cell surface receptors (integrins), heparan sulfate, type IV collagen, and entactin, permitting laminin to mediate interaction between epithelial cells and the ECM by anchoring the cell surface to the basal lamina.
3. **Entactin**, a sulfated adhesive glycoprotein, is a component of all basal (and external) laminae. It binds to laminin linking it to type IV collagen in the lamina densa.
4. **Tenascin**, secreted by glial cells in the developing nervous system, is an adhesive glycoprotein most abundant in embryonic tissues that promotes cell–matrix adhesion and thus plays a role in cell migration.
5. **Chondronectin**, a glycoprotein in cartilage, attaches chondrocytes to type II collagen. It has binding sites for collagen, proteoglycans, and cell surface receptors and plays a role in the development and maintenance of cartilage.
6. **Osteonectin**, a calcium-binding glycoprotein found in bone, is synthesized by osteoblasts. It has binding sites for type I collagen and for integrins of osteoblasts and osteocytes; it functions in bone formation and remodeling and in maintaining bone mass by influencing calcification.

D. Fibronectin receptors are *CAMs*, which belong to the *integrin family of receptors*. They are transmembrane proteins that bind to fibronectin via a specific tripeptide sequence (Arg-Gly-Asp; RGD sequence). These receptors link the glycoprotein fibronectin located outside the cell to cytoskeletal components (e.g., to actin) inside the cell (Fig. 2.2). Additionally, they may activate cell-signaling pathways that determine the cell's behavior, and, conversely, they may cause the cell to enhance or inhibit its ability to bind to the ECM.

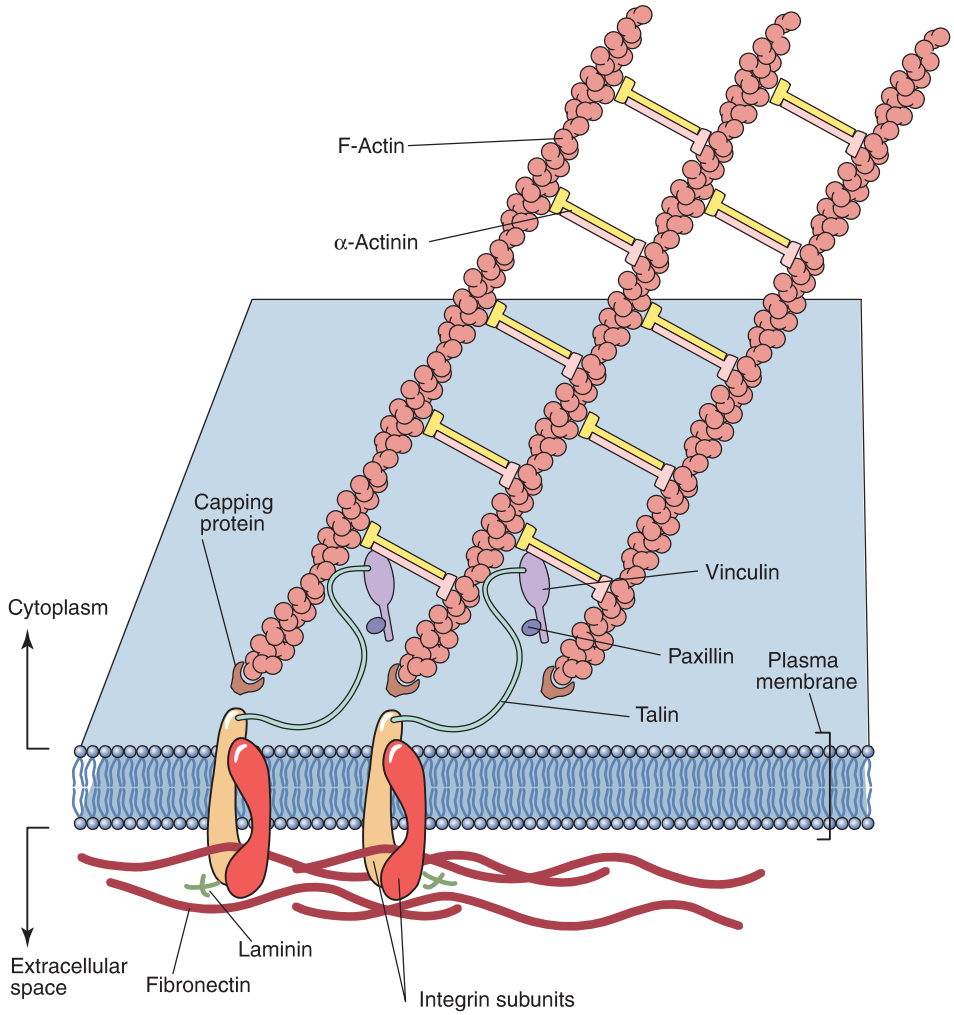


FIGURE 2.2. Integrin receptors such as the fibronectin receptor link molecules outside the cell with components inside the cell. This is common at focal contacts (adhesion plaques), where the integrins serve as transmembrane linkers that mediate reciprocal interactions between the cytoskeleton and the extracellular matrix. (Adapted from Gartner LP. Textbook of Histology. 4th ed. Philadelphia, PA: Elsevier; 2017:50.)

III. FIBERS

A. Collagen, the most abundant ECM structural protein, exists in at least 25 molecular types, which vary in the amino acid sequences of their three α-chains (Table 2.3). The four major categories of collagens are fibril-forming, fibril-associated, network-forming, and transmembrane collagens (collagen-like proteins). Before the discussion of the members of these major categories, the synthesis of fibril-forming and network-forming collagens has to be described.

1. Collagen synthesis and assembly into **fibrils** occurs via a series of **intracellular** and **extracellular** events (Fig. 2.3).

a. Intracellular events in collagen synthesis occur in the following sequence:

(1) The three α-chains of preprocollagen are synthesized **on** the rough endoplasmic reticulum (RER). Hydroxylation of specific proline and lysine residues, catalyzed by hydroxylases and the cofactor vitamin C; glycosylation of specific hydroxylysine residues; and procollagen

table 2.3 Characteristics of Some of the Best-Known Collagen Types

Molecular Type	Cells Synthesizing	Major Locations in Body	Function
I	Fibroblast Osteoblast Odontoblast	Dermis of skin, bone matrix, tendons, ligaments, and fibrocartilage	Resists tension
II	Chondroblast	Hyaline cartilage	Resists intermittent pressure
III	Fibroblast Reticular cell Smooth muscle Schwann cell Hepatocyte	Lymphatic system, cardiovascular system, liver, lung, spleen, intestine, uterus, endoneurium	Forms structural framework in expandable organs
IV	Endothelial cell Epithelial cell Muscle cell Schwann cell	Basal lamina External lamina	Provides support and filtration Acts as scaffold for cell migration
V	Mesenchymal cell	Abundant in most embryonic and adult connective tissue matrices; being incorporated into collagen types I and III Dermal–epidermal junction	Regulates the formation of type I and III collagens
VII	Keratinocyte	Dermal–epidermal junction	Forms anchoring fibrils that secure lamina densa to underlying connective tissue
IX	Chondrocytes	Associated with type II and XI collagen	Binds to type II collagen, affixing it to the proteoglycans of the cartilage matrix
XI	Chondrocytes Fibroblasts	Associated with hyaline and elastic cartilages as well as type I collagen	Acts to stabilize the collagen substructure of the cartilage matrix; forms the core of type I collagen
XII	Fibroblasts Mesenchymal cells	Dermis of skin Placenta	Binds to the surface and assists type I collagen in resisting tensile forces
XIII	Various cell types	In various tissues	Assists in the formation of focal adhesions by binding to fibronectin, integrins, and components of the lamina reticularis
XVII	Epidermis of the skin	Hemidesmosomal component	Binds to keratin with the epithelial cells as well as to integrins and laminin
XVIII	epithelial cells	Basal lamina of the retina of the eye	Proteolysis forms endostatin that inhibits the formation of new blood vessels and induces apoptosis of endothelial cells

triple-helix formation, precisely regulated by **propeptides** (extra nonhelical amino acid sequences) at both ends of each α-chain, all occur **within** the RER. The three α-chains align and coil into a triple helix.

(2) Addition of carbohydrates occurs in the Golgi complex, to which procollagen is transported from RER via transfer vesicles. In the Golgi, carbohydrates are added to complete the oligosaccharide side chains.

(3) Secretion of procollagen occurs by exocytosis after secretory vesicles from the *trans*-Golgi network are guided to the cell surface along microtubules.

CLINICAL CONSIDERATIONS

Scurvy is associated with a **deficiency of vitamin C**. It is caused by the synthesis of poorly hydroxylated tropocollagen, which is unable to form either a stable triple helix or collagen fibrils. **Symptoms** include fatigue, irritability, patches of discolored skin with brittle corkscrew-shaped hair, joint pain, bleeding gums, and eventual tooth loss. Administration of vitamin C, a cofactor with iron in hydroxylation of proline and lysine residues, reverses the disease.

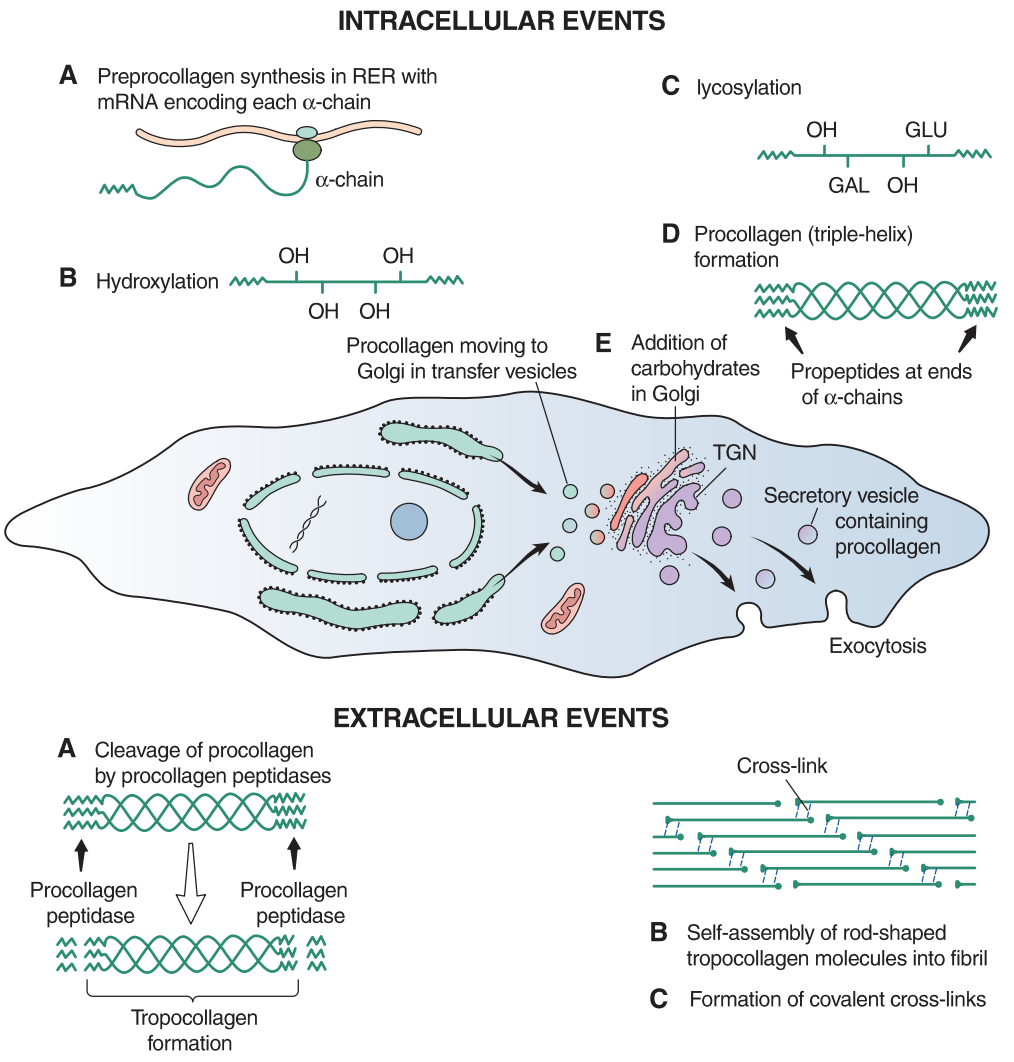


FIGURE 2.3. The intracellular and extracellular steps involved in the synthesis of a collagen fibril. RER, rough endoplasmic reticulum; mRNA, messenger ribonucleic acid; TGN, trans-Golgi network. (Adapted with permission from Junqueira LC, Carneiro J, Kelley RO. Basic Histology. 9th ed. Norwalk, CT: Appleton & Lange; 1998:101.)

b. Extracellular events in collagen synthesis occur in the following sequence:

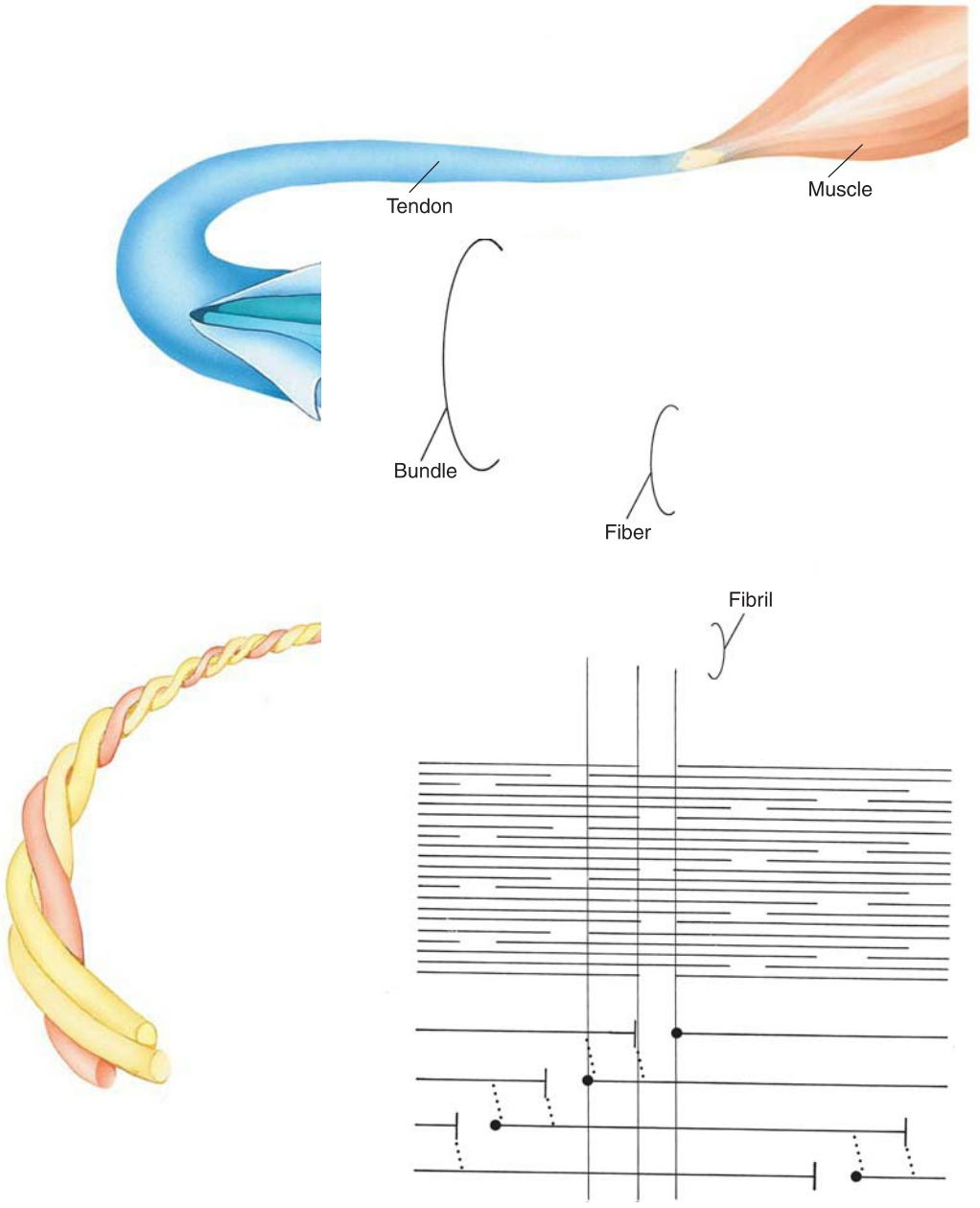
(1) Procollagen peptidases, located on the extracellular aspect of the cell membrane, cleave most of the propeptide sequences at the ends of each α-chain, yielding **tropocollagen** molecules, which self-assemble in longitudinal furrows of the cell membrane.

(a) Fibrils characteristic of fibril-forming collagen are produced with the transverse banding periodicity of 67 nm (especially in types I, II, and III collagen) (Figs. 2.4 and 2.5).

(b) The formation of type I collagen requires a core of type XI collagen as well as the inclusion of type V and type XII collagens.

(c) The formation of type II collagen fibers requires the addition of chondroitin sulfate–enriched type IX collagen fibers.

(2) Covalent bond formation (cross-linking) occurs between adjacent tropocollagen molecules and involves formation of lysine- and hydroxylysine-derived aldehydes. This cross-linking imparts great tensile strength to collagen fibrils.



Each collagen fiber bundle is composed of smaller fibrils, which in turn consist of aggregates of **tropocollagen molecules**. Tropocollagen molecules self-assemble in the extracellular environment in such a fashion that there is a gap between the tail of one molecule and the head of the succeeding molecule of a single row. As fibrils are formed, tails of tropocollagen molecules overlap the heads of tropocollagen molecules in adjacent rows. Additionally, the **gaps** and **overlaps** are arranged so that they are in register with those of neighboring (but not adjacent) rows of tropocollagen molecules. When stained with a heavy metal, such as osmium, the stain preferentially precipitates in the gap regions, resulting in the repeating **light** and **dark** banding of collagen.

FIGURE 2.4. The levels of organization in collagen fibers. As seen by light microscopy, collagen fibers consist of collagen fibrils, which typically reveal a 67-nm cross-banding when observed by electron microscopy. The periodicity along the collagen fibril is due to the precise arrangement of tropocollagen molecules, which overlap each other, producing gap regions where electron-dense stains penetrate and produce a transverse banding across the fibril. (Reprinted with permission from Gartner LP. *Color Atlas and Text of Histology*. 7th ed. Baltimore, MD: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2018.)

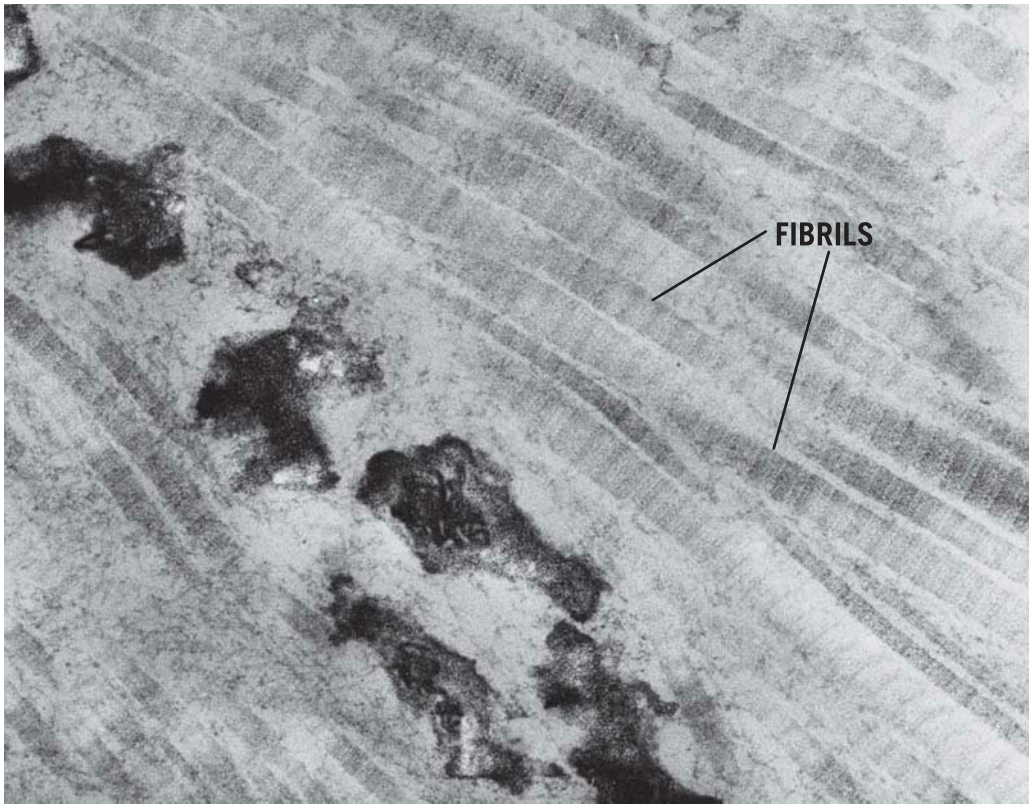


FIGURE 2.5. Electron micrograph showing a number of collagen fibrils with their characteristic 67-nm cross-banding. The large black structures represent calcium phosphate deposits.

CLINICAL CONSIDERATIONS

Ehlers-Danlos type IV syndrome results from mutations in the α1(V) or α2(V) genes that code for two of the α-chains of collagen V. Clinical findings include skin that is thin, translucent, fragile, easily bruised, and sometimes stretchy (elastic); diminished wound healing; and joints that are abnormally flexible and that may be easily dislocated. Patients often present with a rupture of the bowel and/or large arteries, where reticular fibers normally ensheath smooth muscle cells.

2. Synthesis of network-forming collagens, specifically **type IV collagen**, is unique in that it assembles into a meshwork formation rather than into fibrils.
   - **a.** Type IV collagen constitutes most of the **lamina densa** of basal laminae and external laminae.
   - **b.** It differs from other collagen types as follows:
     - **(1)** The propeptide sequences are not removed from the ends of its procollagen molecules.
     - **(2)** Its triple-stranded helical structure is interrupted in many regions.
     - **(3)** It forms head-to-head dimers that interact to form lateral associations, creating a sheet-like meshwork.

CLINICAL CONSIDERATIONS

Alport syndrome is the result of genetic defects in the genes that are responsible for the formation of collagen types III, IV, and V, which result in the abnormal type IV collagen assembly. Because the lamina densa of the basal lamina is formed mostly by type IV collagen, individuals afflicted by Alport syndrome present with glomerulonephritis that results in end-stage kidney disease. These individuals also have hearing disorders and an anomaly of the lens of their eyes known as lenticonus, a bulge that occurs in the lens during development; the consequence of the bulge may be a herniated lens. Because the gene that codes for type IV collagen is located on the X chromosome, Alport syndrome occurs much more frequently in males than in females.

3. **Collagen classes**
   a. **Fibril-forming collagens** (types I, II, III, V, and XI), whose subunits are the tropocollagen molecules, form long, flexible fiber bundles displaying a **67-nm cross-banding**. Their tensile strength is greater than that of stainless steel of the same diameter. Tropocollagen molecules are formed by three α-chains (each composed of about 1,000 amino acids) wrapped around one another. Because every third amino acid in each α-chain is a **glycine**, the smallest of the amino acids, the three chains can form a very tight helix by bending at these amino acids. All three α-chains are rich in **hydroxyproline** and **hydroxylysine** molecules; the hydroxyprolines of each α-chain form tight bonds with each other, assisting in the maintenance of the tight helix, whereas the hydroxylysines bind to each other across neighboring tropocollagen molecules, thus assisting in the formation of collagen fiber bundles.
   b. **Fibril-associated collagens** (types IX and XII) are bound to the surfaces of fibril-forming collagens. They stabilize the collagen framework of the tissues in which they reside by adhering not only to the collagen fibers but also to the molecules of the ground substance. **Type IX collagens** are associated with type II collagens of cartilage and **type XII collagens** are localized on the surface of type I collagens.
   c. **Network-forming collagens** (types IV and VII), unlike the other types of collagen, have procollagen as their subunits. The propeptide sequences at either end of the molecule are not removed by procollagen peptidase in the extracellular environment; therefore, they are unable to assemble in the style of tropocollagen molecules. Hence, they do not form fibers. Instead, the procollagen molecules form head-to-head dimers that interact with each other forming lateral associations, creating a **sheet-like meshwork**. **Type IV collagen** forms the lamina densa of the basal lamina (and external lamina) and **type VII** collagens form the anchoring fibrils that secure the lamina densa to the lamina reticularis of the underlying connective tissue.
   d. **Transmembrane collagens** (types XIII, XVII, and XVIII) are associated with focal adhesions, hemidesmosomes, and the basal laminae, respectively. They are also referred to as collagen-like proteins.

CLINICAL CONSIDERATIONS

Two collagen-associated anomalies

1. **Knobloch syndrome (type I)** is an inherited disease resulting from the malformation of type XVIII collagen. The symptoms include encephalocele, the formation of large brain vesicles that jut out through a defect of the bony skull because of incomplete fusion of the neural tube during embryonic development, as well as sporadic detachment of the retina and nearsightedness that may become evident by the time the child is 1 year old.
2. **Overexpression of type V collagen** has been associated with human breast cancer and cancer of the liver without an accompanying increase in collagen types I and III. Whether this is a causative factor or only a factor that accompanies these cancers is not known.

B. Elastic fibers

1. **Elastic fibers** (Fig. 2.6) may be stretched as much as 150% of their resting length before they break. They have three main components: elastin, fibrillin-1, and fibulin-5, and they are usually associated with type VIII collagen.
   a. **Elastin**, an amorphous structural protein, constitutes 90% of the elastic fibers (elastic sheets). It is rich in the amino acid **lysine**.
      (1) Lysine residues of four different chains form deformable covalent bonds, called **desmosine cross-links**, to create an extensive elastic network. After elastin is stretched and the tensile force is released, the deformed desmosine bonds return to their original shape.
   b. **Fibrillin-1**, a glycoprotein, organizes elastin into fibers and is the main component of the **peripheral microfibrils** of elastic fibers.
      (1) The amino-terminus of one fibrillin-1 interacts with the carboxyl-terminus of another fibrillin-1 molecule to form pencil-like head-to-tail assembly of fibrillin-1 molecules to form microfibrils.
      (2) Fibrillin-1 possesses binding sites for tropoelastin that form cross-links with each other.
      (3) Heparin competes with tropoelastin for binding sites on fibrillin-1, which probably has a regulatory effect on elastic fiber formation.

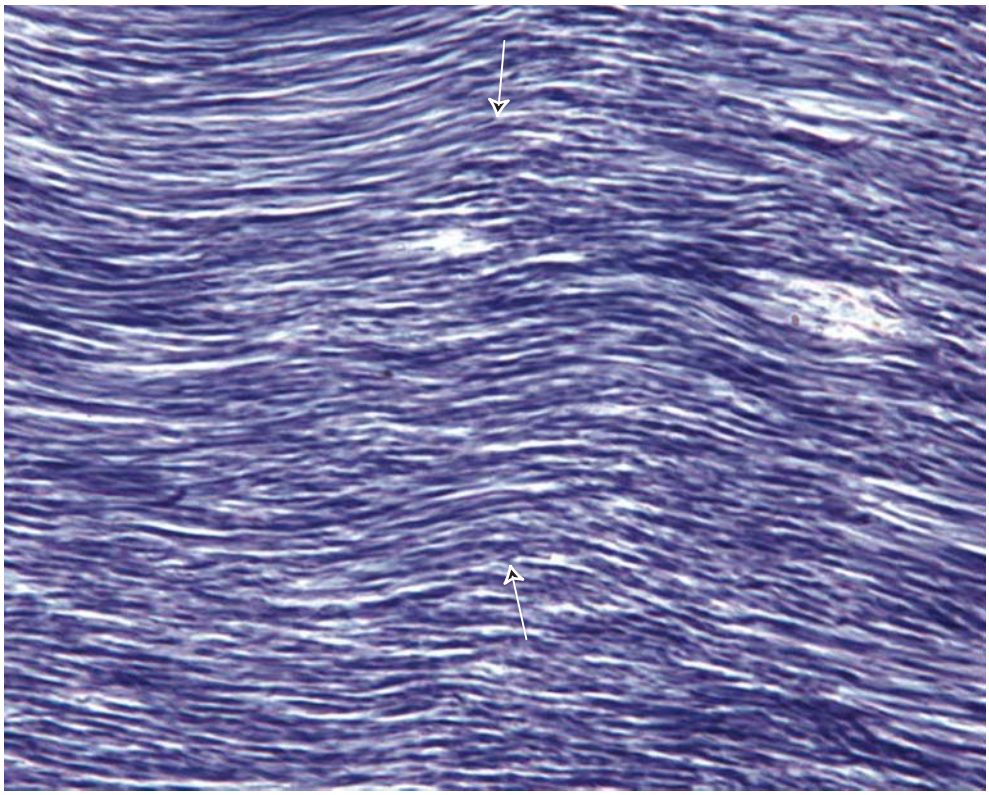


FIGURE 2.6. Dense regular elastic connective tissue. Note that the fibers are short and the ends of the fibers are curled (*arrows*).

   c. **Fibulin-5**, a protein, forms bonds with integrin molecules of cells such as vascular smooth muscle cells and endothelial cells of blood vessels as well as with microfibrils and tropoelastin, and also facilitates the formation of elastic fibers.
      (1) Fibulin-5 is present in a greater concentration during wound healing than in undamaged blood vessels.
   d. **Type VIII collagen** is often associated with elastic fibers, most probably protecting them by limiting the extent of their stretching.

2. **Synthesis of elastic fibers** is carried out by **fibroblasts** in elastic ligaments, **smooth muscle cells** in large arteries, and **chondrocytes** and **chondroblasts** in elastic cartilage.
   a. Synthesis begins with the elaboration of **fibrillin microfibril templates** that are arranged in a parallel array near indented regions of the cell surface.
   b. These cells manufacture and exocytose a soluble form of elastin, known as **tropoelastin**, and fibulin-5, which bind not only to each other but also to fibrillin-1.
   c. Tropoelastin molecules cross-link with each other to form insoluble, mature elastin.
   d. Additional factors, such as heparan sulfate, microfibril-associated glycoproteins, and fibrillin-2, have also been implicated in the assembly of elastic fibers.

CLINICAL CONSIDERATIONS

Marfan syndrome results from mutations in the genes encoding **fibrillin**, a critical component of elastic fibers. Patients with this condition have unusually long, slender limbs and long fingers. In addition, the lens of the eye often dislocates; cardiovascular problems are common; and the aorta may rupture, causing death. Treatment includes drugs that decrease blood pressure and, in severe cases, surgically replacing the aorta.

Review Test

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completion of the statement. Select the ONE lettered answer or completion that is BEST in each case.

The following two questions are based on this scenario:

A medical student goes to the emergency department and is diagnosed with a ruptured bowel, the result of a genetic condition called Ehlers-Danlos type IV syndrome.

1. Which one of the following statements about this patient's condition is true?

(A) He has a defect in the synthesis of mRNA encoding type I collagen.
(B) He has a defect in the genes encoding type IV collagen.
(C) He has defective type V collagen.
(D) He has an increased risk of breaking his bones.
(E) He has a defect in the translation of mRNA for type III collagen.

2. Which other issues should the physician investigate in this patient?

(A) Increased red blood cells count
(B) Low respiratory volume
(C) Barrett esophagus
(D) Glomerular filtration rate
(E) Aneurysm of large arteries

The following three questions are based on this scenario:

A patient goes to her physician with complaints of fatigue; irritability; painful joints; patches of discoloration on her skin with brittle, cork-screw-shaped hair; and swollen and bleeding gums. Upon questioning, she tells her physician that she started a new diet about 5 months ago that consists only of meat and various types of cheeses.

3. Based on her symptoms, which of the following was missing from her diet?

(A) Amino acids
(B) Ascorbic acid
(C) Lipids
(D) Folic acid
(E) Calcium

4. What is the function of the missing item? It is a/an

(A) essential amino acid.
(B) calcium blocker.
(C) cofactor.
(D) enzyme in vitamin B synthesis.
(E) enzyme in triglyceride formation.

5. How does the missing item relate to her joint pain? It causes

(A) defective cartilage formation.
(B) calcium deposits in the joint.
(C) reduced synovial fluid volume.
(D) leakage of blood into the joints.
(E) decreased lipid that increases friction.

The following two questions are based on this scenario:

A 12-year-old boy was admitted to the hospital because a superficial abrasion that occurred during a soccer match became excessively painful, swollen, and hot to the touch. Additionally, he had high fever and diarrhea and was vomiting. He was diagnosed with necrotizing fasciitis.

6. Which of the following is responsible for the rapid progression of this condition?

(A) Excess type V collagen
(B) Reduced type XVIII collagen
(C) Defective fibrillin
(D) Hyaluronidase
(E) Procollagen peptidase

7. Why did he have high fever and why was the wound hot to the touch?

(A) The pathogenic bacteria altered his collagen levels.
(B) The pathogenic bacteria elicited an inflammatory response.
(C) The vomiting increased his core temperature.
(D) The extreme pain increased his metabolic levels.
(E) The swelling induced stretch receptors to increase his peripheral temperature.

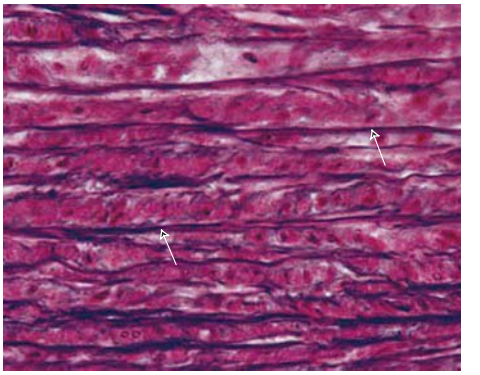
8. What is a glycoprotein across which fibroblasts migrate during wound healing?

(A) Fibrillin
(B) Fibronectin
(C) Elastin
(D) Entactin
(E) Laminin

9. Which event in collagen synthesis occurs outside of the cell?

(A) Synthesis of preprocollagen
(B) Hydroxylation of lysine residues
(C) Triple-helix formation
(D) Carbohydrate addition to procollagen
(E) Cleavage of procollagen by procollagen peptidases

10. This question is based on the accompanying photomicrograph and the patient scenario below:



This photomicrograph is from a normal area of a biopsy of a patient suffering from Marfan syndrome. The arrows indicate the defective structure in the abnormal area of the biopsy. That structure is composed of

(A) type I collagen.
(B) type II collagen.
(C) elastic fibers.
(D) fibronectin.
(E) laminin.

Answers and Explanations

1. **E.** Ehlers-Danlos type IV syndrome is associated with a defect in the synthesis and translation of mRNA for type III collagen.
2. **E.** Large arteries are also affected in Ehlers-Danlos type IV syndrome because their walls are weak and often present with aneurysms.
3. **B.** Ascorbic acid (vitamin C) has been missing from her diet for more than 5 months and because of that the patient is suffering from scurvy. She should be counseled to take vitamin C supplements, and, she should be advised to eat a balanced diet.
4. **C.** Ascorbic acid (vitamin C) and iron are cofactors required for the hydroxylation of proline and lysine residues necessary for the integrity of collagen fibers.
5. **D.** Blood vessels become leaky because of the defective collagen in their walls. That is the reason that the patient has swollen and bleeding gums. Blood also leaks into joints, making them very painful.
6. **D.** Hyaluronidase is an enzyme that cleaves hyaluronic acid, thus permitting the rapid movement of ECF through the connective tissue matrix. Some bacteria, such as *Staphylococcus aureus* and *Streptococcus pyogenes*, can invade the broken skin and release hyaluronidase, which permits these bacteria to spread at a very rapid rate through the connective tissue. They release toxins that can cause major and often life-threatening conditions.
7. **B.** The presence of pathogenic bacteria in his connective tissue induced an inflammatory response that resulted in high temperature and heat at the area of inflammation.
8. **B.** Fibronectin forms tracks along which cells migrate. During wound healing in connective tissue, fibroblasts adhere to fibronectin in blood clots, facilitating the healing process.
9. **E.** In the extracellular space, peptidases cleave off end sequences of procollagen to yield tropocollagen, which self-assembles to form collagen fibrils.
10. **C.** This is a light micrograph of the aorta, and the structures indicated by the arrows are known as fenestrated membranes that are composed of elastic fibers. Marfan syndrome is due to the mutation in the gene that codes for fibrillin, a critical component of elastic fibers.

chapter 3

Epithelia and Glands

I. OVERVIEW—EPITHELIA

A. Structure. Epithelia originate from all three embryonic germ layers; they line the internal and cover the external surfaces of the body except in specialized regions such as tooth surfaces and articular cartilages.

1. An epithelium consists of a **sheet of cells** lying close together exhibiting minimal extracellular space. Cells of an epithelial sheet display biochemical, functional, and structural domains that confer **polarity**; thus, these cells are said to have **apical**, **lateral**, and **basal epithelial domains** (or as some authors prefer **basolateral domain**).
2. Epithelia are **avascular**, thus receive nourishment by diffusion through the **basement membrane** that separates them from the underlying connective tissue.

B. Classification. Epithelia are classified into various types based on the **number** of cell layers (one cell layer is **simple**; more than one is **stratified**) and the **shape of the superficial cells** (Table 3.1 and Fig. 3.1). Therefore, all cells composing a simple epithelium contact the basement membrane whereas in stratified epithelia cells in the deepest layer only contact the basement membrane. **Pseudostratified** epithelia give the appearance of having multiple cell layers, but they are composed of a single cell layer only, as evidenced by the fact that all cells that compose this type of epithelium are in contact with the basement membrane (Fig. 3.2A and B).

table 3.1 Classification of Epithelia

Type	Shape of Superficial Cell Layer	Typical Locations
One cell layer		
Simple squamous	Flattened	Endothelium (lining of blood vessels), mesothelium (lining of peritoneum and pleura)
Simple cuboidal	Cuboidal	Lining of distal tubule in kidney and ducts in some glands, surface of ovary
Simple columnar	Columnar	Lining of intestine, stomach, and excretory ducts in some glands
Pseudostratified	All cells rest on basal lamina, but not all reach the lumen; thus, the epithelium appears falsely stratified	Lining of trachea, primary bronchi, nasal cavity, and excretory ducts in parotid gland
More than one cell layer		
Stratified squamous (not keratinized)	Flattened (nucleated)	Lining of esophagus, vagina, mouth, and true vocal cords
Stratified squamous (keratinized)	Flattened (without nuclei)	Epidermis of skin
Stratified cuboidal	Cuboidal	Lining of ducts in sweat glands
Stratified columnar	Columnar	Lining of large excretory ducts in some glands and cavernous urethra
Transitional	Dome-shaped (when relaxed), flattened (when stretched)	Lining of urinary passages from renal calyces to the urethra

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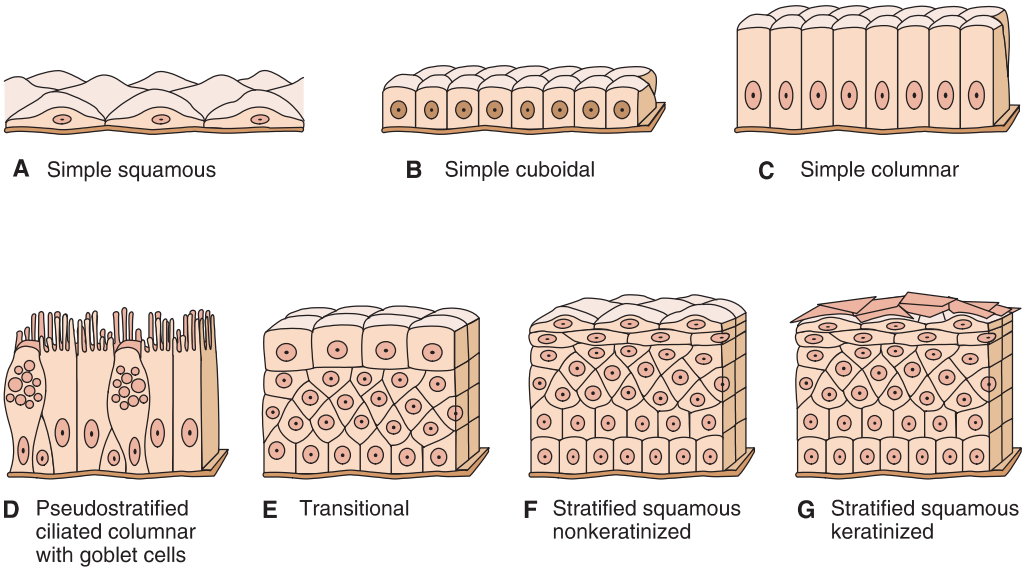


FIGURE 3.1. Classifications of epithelia.

C. **Function.** Epithelia transport, absorb, secrete, protect, and display selective permeability.

1. **Transcellular transport** of molecules occurs mostly by
   a. **Diffusion** (e.g., oxygen) across the epithelial cells of lung alveoli and capillaries
   b. **Carrier protein–mediated transport** (e.g., amino acids) across intestinal epithelia
   c. **Vesicle-mediated transport** (e.g., immunoglobulin A) by intestinal epithelial cells
2. **Absorption** occurs via **endocytosis** or **pinocytosis** by cells of various organs (e.g., the proximal convoluted tubule of the kidney).
3. **Secretion** of various molecules (e.g., hormones) occurs by **exocytosis**.
4. **Protection** from abrasion and injury is provided by some epithelia, such as the **epidermis** of the skin.
5. **Selective permeability** restricts what may or may not cross the cell membrane resulting in fluids with different compositions and concentrations to exist on either side of an epithelial layer (e.g., kidney).

CLINICAL CONSIDERATIONS

Burn injuries, lesions caused by contact with heat, friction, caustic agents, electricity, or exposure to radiation, are classified into three categories depending on the number of cell layers that are damaged.

1. **Superficial (first-degree) burns** are lesions where the damage is limited to the superficial layers of the **epithelium** (usually the epidermis of the skin or the epithelial lining of the mouth). There is pain, swelling, and redness but no blisters are formed. Mitotically active cells remain viable in the deeper layers of the epidermis, which divide and replace the damaged or destroyed cells.
2. **Partial-thickness (second-degree) burns** are of two types: **superficial partial thickness** and **deep partial thickness.**
   a. **Superficial partial-thickness burns** affect not only the superficial layers but also deeper layers of the epithelium and the papillary layer of the dermis (superficial connective tissue layer of the skin). It is very painful, there is swelling and redness, *and* blisters are formed.
   b. **Deep partial-thickness burns** affect the entire thickness of the epithelium and partial thickness of the reticular layer (deep layer) of the dermis. Instead of pain there is pressure, blisters may or may not form, and the lesion is white to yellowish in color.
3. **Full-thickness (third-degree) burns** affect the entire thickness of both the epithelium and the dermis. Because the nerves of the skin are destroyed, there is minimal pain. The lesion is white to light brown in color.

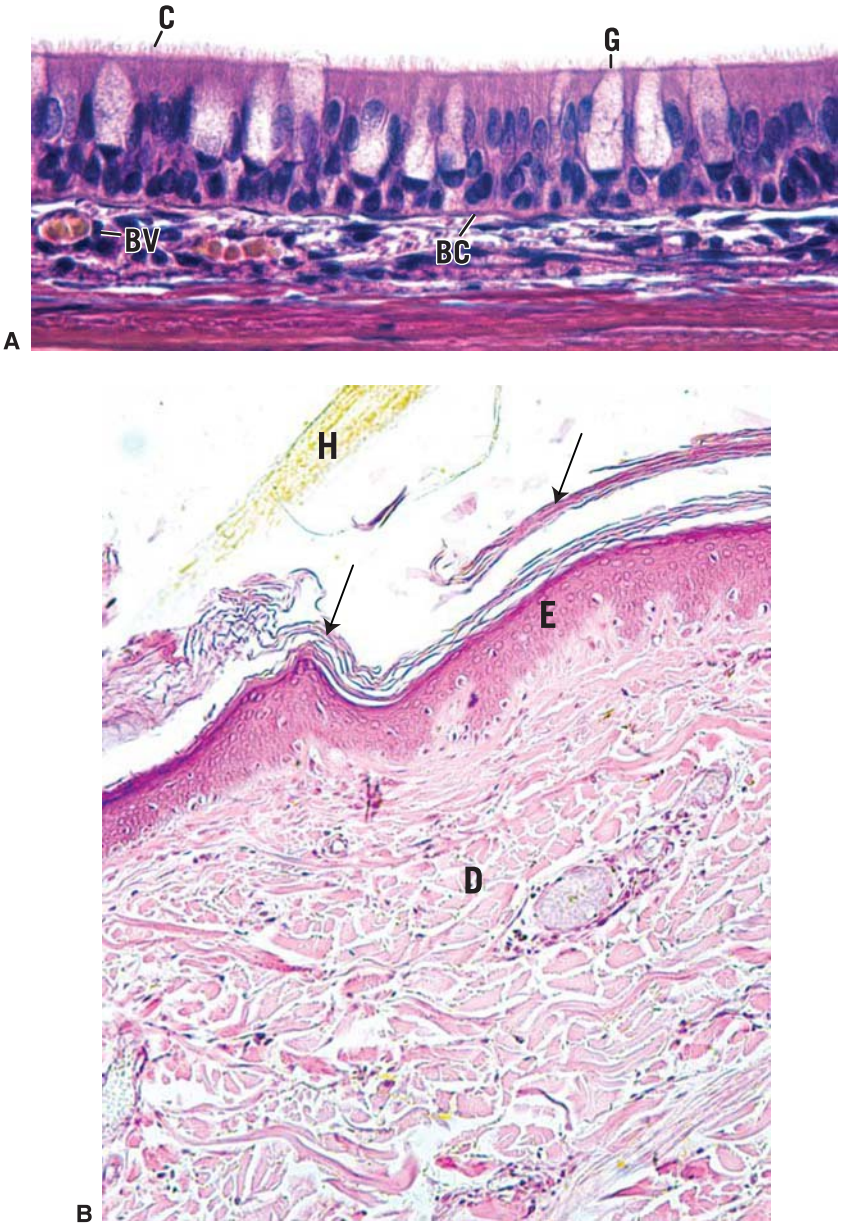


FIGURE 3.2. **A.** A light micrograph of pseudostratified ciliated (C) columnar epithelium with goblet cells (G) lining the trachea. All of the cells in this epithelium rest on the basal lamina (note the basal cell [BC]), but not all of them extend to the lumen, giving a falsely stratified appearance. Blood vessels (BV) containing red blood cells are seen in the underlying connective tissue. **B.** A light micrograph of thin skin. Note that the epidermis is a stratified squamous keratinized epithelium (E). The *arrows* point to the keratin layer that is being sloughed off, and a hair shaft (H) is evident. The connective tissue that underlies the epidermis is known as the dermis (D).

II. LATERAL EPITHELIAL SURFACES (Fig. 3.3)

The lateral surfaces contain specialized molecules that form **junctional complexes** that assist epithelial cells to adhere to each other and to restrict movement of materials between adjacent cells (**paracellular route**) into and out of the connective tissue lined/covered by the epithelium.

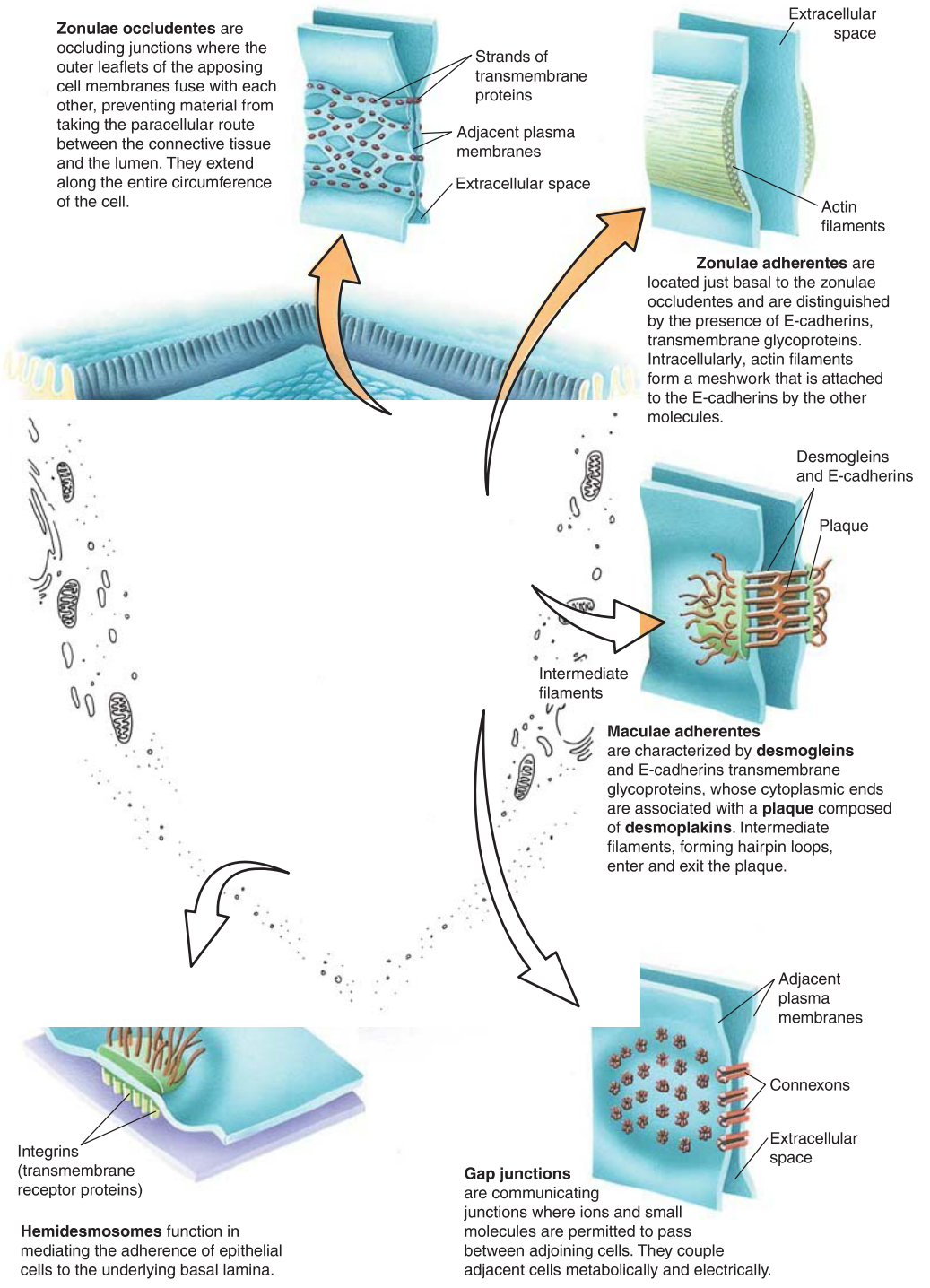


FIGURE 3.3. A diagram illustrating the location and features of junctional specializations found in epithelial cells: the junctional complex, the desmosome, the gap junction, and the hemidesmosome. (From Gartner LP. *Color Atlas of Histology*. 7th ed. Baltimore, MD: Lippincott, William & Wilkins; 2018:42.)

A. The junctional complex is an intricate arrangement of membrane-associated *cell adhesion molecules* (*CAMs*) that function in cell-to-cell attachment of columnar epithelial cells. It corresponds to the terminal bar observed in epithelia by light microscopy and consists of three distinct components made visible by electron microscopy.

1. Occluding junction

a. The **tight junction (zonula occludens;** plural: zonulae occludentes) is a zone that surrounds the entire apical perimeter of adjacent cells and is formed by **fusion of the outer leaflets** of the plasma membranes of adjacent cells (Fig. 3.3 and Table 3.2).

(1) Viewed in freeze-fracture preparations, the tight junction appears as a branching anastomosing network of **intramembrane strands** (**ridges**) on the inner leaflet of the plasma membrane (facing the cytoplasm [P-face]) and **grooves** on the corresponding external E-face, the inner aspect of the outer leaflet (Fig. 3.3). The strands consist of **transmembrane proteins** of one cell that attach to **transmembrane proteins** of the adjacent cell and seal off the extracellular space.

(2) The four groups of these transmembrane proteins are

(a) Claudins, whose extracellular moieties create a physical barrier, prevent the movement of material between the cells, but their small aqueous pores allow water and small ions to penetrate this barrier.

(b) Occludins are present in most, but not all epithelial cell tight junctions; their function is not understood.

(c) Nectins are also present in the zonula occludens and their extracellular domains form a part of the physical barrier.

(d) Junctional adhesion molecules' extracellular domains also form a part of the physical barrier.

(3) These four proteins are reinforced intracellularly by **actin filaments** (**F-actin**) of the cytoskeleton and by the three **zonula occludens proteins** (**ZO-1**, **ZO-2**, and **ZO-3**), as well as a fourth protein, **afadin**. All four intermediary proteins are interposed between the F-actin and the transmembrane proteins, forming a strong bond that maintains the integrity of the tight junction.

table **3.2** Junctional Complex Components

Junction	Distance Between Cells	Components	Functions
Zonula occludens (surrounds entire cell)	0 nm	Claudins (tmp)	Close paracellular route
		Occludins (tmp)	?
		Nectins (tmp)	Close paracellular route
		JAMs (tmp)	?
		Actin (icp)	Provide support for tmps
		ZO-1, ZO-2, ZO-3 (icp)	Provide support for tmps
		Afadin (icp)	Provide support for tmps
Zonula adherens (surrounds entire cell)	10–20 nm	E-cadherins (tmp)	Adhere to its counterpart
		Actin (icp)	Provide support for tmps
		α-Actinin (icp)	Binds to actin filaments
		Vinculin (icp)	Binds actin to catenin
		Catenin (icp)	Binds to vinculin and cytoplasmic aspect of E-cadherin
Desmosome (occurs in discrete spots; does not surround the entire cell)	30 nm	Desmogleins (tmp)	Adhere to its counterpart to form extracellular core
		Desmocollins (tmp)	Adhere to its counterpart to form extracellular core
		Plakoglobins (icp)	Bind to desmogleins and desmocollins (form outer dense plaque)
		Plakophilins (icp)	Bind to desmogleins and desmocollins (form outer dense plaque)
		Desmoplakins (icp)	Bind to plakoglobins and plakophilins (form outer dense plaque)
		Keratin	Intermediate filaments that bind to desmoplakins (form inner dense plaque)

icp, intracellular proteins; JAMs, junctional adhesive molecules; tmp, transmembrane proteins/glycoproteins.

(4) Additionally, tight junctions prevent intermingling of the transmembrane proteins of the apical with those of the lateral domains. This ability (its tightness) is directly related to the number and complexity of the intramembrane strands and to the function of the epithelia housing the particular tight junction.

(5) **Fascia occludens** (plural: fasciae occludentes), a ribbonlike area of fusion between transmembrane proteins on adjacent **endothelial cells** lining capillaries, is analogous to the zonula occludens but does not encircle the perimeter of the entire cell.

2. **Anchoring junctions** of epithelial cells (Fig. 3.3 and Table 3.2) consist of four types: two on the cell's lateral domain, **zonula adherens** (plural: zonulae adherentes) and **desmosome** (**macula adherens**; plural: maculae adherentes), and two, discussed in the section below, on the cell's basal domain, namely **hemidesmosomes** and **focal adhesions**.

a. The **zonula adherens**, located just basal to and reinforcing the zonula occludens, surrounds the entire perimeter of epithelial cell. It is characterized by a 10- to 20-nm separation between the adjoining cell membranes where the extracellular portions of the transmembrane glycoprotein **E-cadherin** (***E****pithelial* ***ca****lcium-****d****ependent ad****herin****g*; **transmembrane linker protein**) molecules contact their counterpart of the adjoining cell.

(1) **Actin molecules**, that form a mat of **filaments** on each of the cytoplasmic surfaces of the zonulae adherentes, are linked to each other via the actin-binding proteins **α-actinin**. They are also linked, via **vinculin**, to the protein **catenin**, which furthermore binds to the intracellular portion of the **E-cadherin molecules**. Thus, E-cadherin molecules are reinforced, indirectly, by the actin filaments of the cytoskeleton.

(2) The extracellular moieties of E-cadherins of adjacent cells face each other in the extracellular space and, in the presence of Ca^{2+} ions, bind to each other, facilitating **adhesion** of adjacent cells to each other.

(3) **Fasciae adherentes**, ribbonlike adhesion zones in the **intercalated disks** of cardiac muscle, are analogous to zonulae adherentes, but they do not surround the entire perimeter of the cardiac muscle cells.

b. **Desmosomes** (**maculae adherentes**) are small, discrete, disk-shaped **adhesive sites** (Fig. 3.3 and Table 3.2). Desmosomes are commonly present both at the junctional complex and along the lateral membrane, where they aid in the adherence of epithelial cells to each other.

(1) Desmosomes are characterized by having five regions: two intracellular regions in ***each*** cell, namely the **inner dense plaque** (adjacent the cytoplasm) and the **outer dense plaque** (adjacent the inner aspect of the plasmalemma), and an extracellular region, known as the **extracellular core**, located in the middle of the 30-nm-wide space between the two cells.

(2) The extracellular moieties of the transmembrane glycoproteins, **desmogleins** and **desmocollins**, members of the E-cadherin superfamily, of one cell contact desmogleins and desmocollins of the other cell in the extracellular space. In order for these glycoproteins to form strong adhesive bonds with their counterparts, Ca^{2+} ions must be present. These extracellular moieties of desmogleins and desmocollins of each cell form the **extracellular core** and attach the two cells to each other.

(3) The intracellular moieties of desmogleins and desmocollins form bonds with the desmosomal plaque proteins **plakoglobins** and **plakophilins**. Additional large proteins, known as **desmoplakins**, contact both plakoglobins and plakophilins, and together they form the **outer dense plaque** that presses against the cytoplasmic aspect of each cell membrane.

(4) The tails of desmoplakins extend farther into the cytoplasm where they contact and form bonds with the **keratin intermediate filaments** of the epithelial cell. This region of bonding between the desmoplakins and the intermediate filaments forms the **inner dense plaque**, and here the cytoskeleton is affixed to the site of adherence.

B. Gap junctions (communicating junctions; nexus) are not part of the junctional complex and are frequent components of certain tissues other than epithelia (e.g., central nervous system, cardiac muscle, and smooth muscle).

1. Gap junctions are small aqueous pores that are inserted into the plasma membranes that **couple adjacent cells** metabolically and electrically (Fig. 3.3).

2. A gap junction is composed of subunits, called **connexons** (**hemichannels**), which extend beyond the cell surface into the **gap** (a 2-nm-wide extracellular space). Two connexons, one in the

plasma membrane of each adjacent cell contacting each other in the intercellular space, form a single **gap junction channel**.

a. **Connexons** consist of six subunits (known as **connexins**), which are arranged radially around a central channel with a diameter of 1.5 nm.
b. Precise **alignment** of connexons on adjacent cells produces a junction where they form **cell-to-cell channels** permitting the passage of ions and small molecules with a molecular weight of less than 1 kDa but preventing these molecules from escaping into the extracellular space.
c. Because of the different types of connexons, depending on the amino acid sequence of their connexins, gap junctions may be homotypic or heterotypic.
d. Connexins may alter their conformation to shut off communication between cells, especially if one of the cells is dying.
e. In places, as many as 10,000 gap junction channels may be clustered together to form a **gap junction** where exchange of ions and small second messenger molecules may occur.
f. The gap junction channels in the center of the gap junction are the oldest whereas the gap junction channels at the periphery are the newest. Amazingly, gap junction channels have a lifespan of only about 2 hours.
g. Small clusters of gap junction channels at the center of the gap junction are removed en masse as small membranous vesicles, known as **connexosomes**, and are degraded in lysosomes.
h. New hemichannels, delivered to the periphery of the gap junctions, match up with newly delivered hemichannels of the adjacent cell to form new connexons, thus maintaining the original size of the gap junction.
i. Connexons are in abundant supply where intercellular communication and coordination is essential such as in smooth and cardiac muscles, nerves, and certain epithelia.

CLINICAL CONSIDERATIONS

A number of anomalous conditions, such as deafness, epilepsy, cataracts, and cardiac pathologies have been shown to be due to mutations in one or more genes that codes for connexins (Cxs).

1. Among these is **Charcot–Marie–Tooth disease**, an inherited condition, which is due to a mutation in the gene that codes for protein Cx32 of hemichannels (connexons) located in myelin sheaths. The progressive decrease in the number of gap junction channels results in the degradation of the myelin sheath, resulting in degeneration of the affected nerve and atrophy of the muscles served by those nerves. Most of the muscles affected initially are those of the lower limbs, and the patient exhibits walking difficulties, tripping, stumbling, and falling. Many of the affected individuals show evidence of an unusual gait, lifting their feet higher than necessary. Their lower leg muscles show signs of atrophy. With disease progression, the muscles of the upper limb become involved with a gradual decrease in manual dexterity. Fortunately, the condition is not fatal, and affected individuals have a normal life span.
2. Another condition, **oculodentodigital dysplasia** (**ODDD**), affects more than a single component and is due to as many as 70 different mutations in the gene coding for protein Cx43 of hemichannels. These mutations range from the formation of connexins that cannot insert into the cell membrane to the formation of normal-appearing connexins that either cannot form functioning hemichannels or, if they do, they cannot couple with hemichannels of the adjacent cell. Patients with ODDD exhibit a number of conditions including microphthalmia as well as additional ocular problems resulting in loss of eyesight; small teeth with poorly calcified enamel resulting in numerous cavities and loss of teeth; and syndactyly of some fingers and toes.
3. **Deafness** has been shown to result from mutations in the genes coding for proteins Cx26 and Cx30. Although the reason for deafness is not known, it has been suggested that the defective connexons are unable to transmit certain second messenger molecules necessary for the activation of some cells of the organ of Corti.

C. **Lateral interdigitations (plicae) are irregular fingerlike membrane projections that *interlock* adjacent epithelial cells.** These lateral interdigitations are most frequently present in cells that function in fluid and/or electrolyte transport (e.g., epithelial lining of the intestines; proximal tubules of the kidney).

III. BASAL EPITHELIAL SURFACES

A. The basement membrane is a thin, flexible, PAS-positive (i.e., it stains purplish with periodic acid–Schiff reagent) acellular structure that is consistently interposed between epithelium and the underlying connective tissue. The thickness of the basement membrane depends on its location, so that it is much thicker in thick skin than in the lining of the trachea, but on the average is usually 0.3 μm wide. An analogous structure, the **external lamina**, envelops skeletal and smooth muscle cells, fat cells, and Schwann cells. The basement membrane, when viewed with the electron microscope, is resolved to be composed of two layers, the **basal lamina**, approximately 100 nm in thickness, and the **lamina reticularis**, which is at least 200 nm in thickness (Fig. 3.4). *Recently many authors have started to use the terms* basal lamina *and* basement membrane *as synonyms.*

1. **The basal lamina** is manufactured by the cells of the **epithelial layer** and is composed of two regions, the electron-lucent **lamina lucida**, which is in direct contact with the basal plasma membrane of the epithelial cells, and the electron-dense **lamina densa** that is located between the lamina lucida and the lamina reticularis.
2. The basement membrane has a variety of functions that include
   - **a.** Providing **support** for the epithelium overlying the connective tissue
   - **b.** Facilitating the **adhesion** of epithelium to the connective tissue
   - **c.** **Blocking** certain cells from crossing it
   - **d.** **Conferring** polarity on certain cells
   - **e.** Acting as a molecular **filter** as well as a platform along which cells can **migrate**
   - **f.** Providing signals for cells to **differentiate** and **proliferate**
   - **g.** Providing capabilities for the **regeneration** of neuromuscular junctions
3. *Many authors now believe the lamina lucida to be a fixation artifact and suggest that the* ***lamina densa*** *constitutes the entirety of the basal lamina. However, the research results are not universally accepted; therefore, in this textbook, both components are detailed.*
   - **a.** **Lamina lucida**, the electron-lucent component of the basal lamina, is approximately 50 nm wide and is composed of the extracellular regions of the laminin receptors, **integrin** and **dystroglycan molecules** of the basal plasma membrane. The proteoglycans, **laminin** and **entactin**, are also components of the lamina lucida although they coat the epithelium-faced surface of the adjacent lamina densa. Therefore, the integrins and dystroglycans form bonds with the laminin in the lamina lucida and their intracytoplasmic regions form bonds with components of the cytoskeleton, specifically with **talins** and **α-actinins**. In this fashion, the basal plasma membrane becomes affixed to the lamina lucida. *If one considers the lamina*

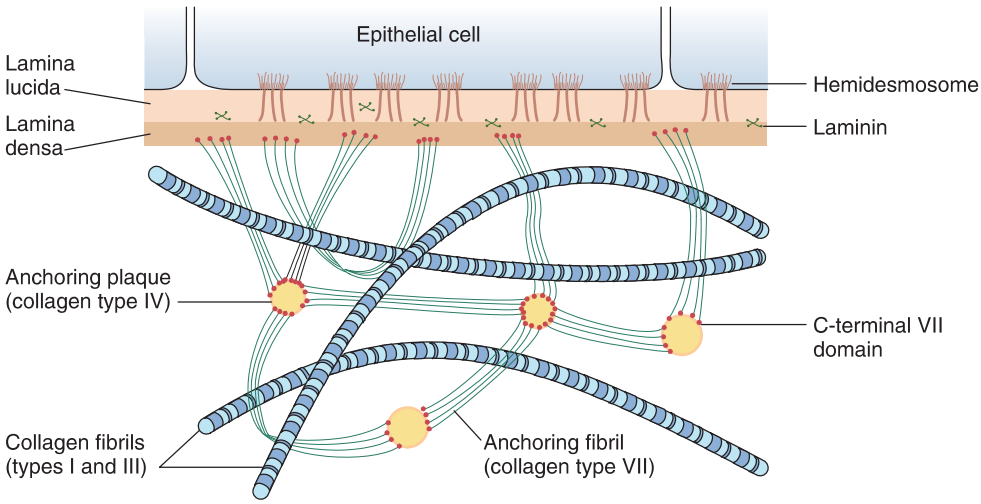


FIGURE 3.4. Basal specializations beneath an epithelium. (Adapted with permission from Keene DR, Sakai LY, Lunstrum GP, et al. Type VII collagen forms an extended network of anchoring fibrils. *J Cell Biol.* 1987;104:611.)

lucida to be an artifact, the components indicated above are still present, but on the epithelial surface of the lamina densa.

b. The **lamina densa** is a 50-nm-thick, dense, flexible feltwork of **type IV collagen** that is interposed between the lamina lucida and the lamina reticularis.

(1) On the lamina lucida side, the lamina densa is coated not only with laminin and entactin but also by **perlacan**, a proteoglycan that is richly endowed with the glycosaminoglycans heparan sulfate. Laminin binds not only to the integrins and dystroglycans but also to **heparan sulfate** of perlacan and to type IV collagen of the lamina densa. Moreover, entactin also binds to both laminin and type IV collagen, and in this fashion a strong adhesion is formed between the lamina lucida and the lamina densa ensuring that the sheath of epithelial cells is firmly attached to the basal lamina.

(2) The surface of the lamina densa that faces the lamina reticularis is also coated by **perlacan** as well as another proteoglycan, **fibronectin**, that is synthesized by **fibroblasts** of the connective tissue. (Another type of fibronectin is present in blood and some other body fluids, manufactured by cells of the liver; see Chapter 5).

(3) Some cells, such as fibroblasts, are unable to penetrate the lamina densa, whereas others, such as lymphocytes and macrophages, possess specific enzymes, **collagenases**, which form small holes in the lamina densa, providing a tunnel so that these cells can migrate from the connective tissue into the epithelium.

c. The **lamina reticularis** is usually 200 nm or more in thickness and is composed of **type III collagen**, **type VII collagen** (**anchoring fibrils**), **type XVIII collagen**, and some **type I collagen** fibers as well as **microfibrils** (composed of the protein **fibrillin**). Fibronectin binds to the various types of collagen fibers as well as to the **heparan sulfate** moieties of perlacan. Additionally, type VII collagen fibrils and microfibrils bind to various components of the lamina reticularis, thereby further securing the lamina densa to the lamina reticularis. Type I and type III collagen fibers loop up from the connective tissue, tethering the lamina reticularis to the superficial surface of the connective tissue. All of these bonds and interactions firmly attach the epithelium to the connective tissue via the various macromolecular components of these structures.

CLINICAL CONSIDERATIONS

Mutations in the genes coding for laminin and/or for type XVII collagen result in the reduced ability of the epithelium to adhere to the basement membrane. This condition, **junctional epidermolysis bullosa** (**JEB**), causes blistering of the skin. It also causes blistering of the mucosa of the trachea, oral cavity, and esophagus. The two types of JEB include a more serious condition (Herlitz JEB) and the less serious (non-Herlitz JEB). In infants suffering from **Herlitz JEB** the mutation is in the genes coding for laminin and in this case the blistering may be widespread resulting in the formation of denuded areas of the skin, trachea, oral cavity, and the alimentary canal with subsequent formation of granulation tissue. Individuals affected to such a high degree by JEB experience breathing complications, nutritional deficiency, and multiple infections with a lifespan of less than 2 years. **Non-Herlitz JEB**, in which the mutation is in the gene coding for type XVII collagen, is a much milder condition because only some regions of the body are affected and these individuals have a normal lifespan.

B. Two additional components of the basal domain of the cell membrane, the anchoring junctions *focal adhesions* and *hemidesmosomes*, also participate in the adhesion mechanism between the epithelium and the connective tissue.

1. Focal adhesions are regions of relatively weak anchoring junctions that assist in the attachment of the epithelium to the basal lamina. The principal components are clusters of transmembrane proteins, α- and β-**integrins**, whose cytoplasmic moieties are attached to **actin filaments** of the cytoskeleton via the intracellular anchorage proteins **α-actinin**, **talin**, **paxillin**, and **vinculin** and their extracellular regions are attached to **laminin** and **fibronectin** of the basal lamina. Focal adhesions may be attachments of long duration but mostly they are formed as cells migrate along the basal lamina surface and continuously detach and reattach during their movement. Both the attachment and detachment are dynamic processes that occur because of intracellular and/or

extracellular signals that alter the three-dimensional conformation of the integrin molecules causing them to form or break bonds with the intracellular anchorage proteins and with the matrix proteins of the basal lamina.

2. **Hemidesmosomes** are specialized anchoring junctions whose morphology resembles that of a half of a desmosome. However, instead of attaching cells to each other, hemidesmosomes mediate strong **adhesion** of epithelial cells to the underlying extracellular matrix (Fig. 3.3 and Table 3.3). Unlike focal adhesions, hemidesmosomes are mostly of longer duration and provide a firmer attachment of the cell to the basal lamina. Moreover, instead of binding to actin filaments of the cytoskeleton, they are bound to the more robust intermediate filaments.
   - **a.** Hemidesmosomes are of two types. The **classical type** (**type I hemidesmosome**) is located in the stratum basale of skin, in the lining of the esophagus, in the masticatory and lining mucosae of the oral cavity, as well as in the cells of pseudostratified epithelia of structures such as the trachea and is more complex than the **type II hemidesmosome**, present mostly in the simple columnar epithelia of the intestinal lining.
     - **(1)** Type I hemidesmosomes have a dense cluster of transmembrane proteins **$\alpha_6\beta_4$ integrin** whose intracytoplasmic moieties bind to the protein **erbin** and the **plakin** proteins **plectin** and **bullous pemphigoid antigen 230** (**BP230**).
       - **(a)** These two plakin proteins connect $\alpha_6\beta_4$ integrins to the **intermediate filaments** (**keratin-5** and **keratin-14**, also known as **tonofilaments**). Erbin assists the binding of the integrin molecule to BP230.
       - **(b)** Two additional proteins are associated with the α_6 component of the integrin, namely the *transmembrane collagen*, **type XVII collagen** (also known as **bullous pemphigoid antigen 180**), and **cluster of differentiation protein 151** (**CD151**).
       - **(c)** Type XVII collagen binds intracellularly to both α_6 component of the integrin and to plectin and extracellularly to α_6 component of the integrin and to laminin of the basal lamina. The extracellular moieties of $\alpha_6\beta_4$ integrins also bind to the **laminins** and **type IV collagens** of the basal lamina.
       - **(d)** **CD151** functions to ensure that enough integrin molecules are recruited to the area so that hemidesmosome formation can occur. The intracytoplasmic components of the hemidesmosome form an electron-dense, plaquelike structure that resembles but is different from the outer dense plaque of a desmosome.
     - **(2)** Type II hemidesmosomes are much simpler than the classical hemidesmosomes, in that they are composed only of the dense cluster of transmembrane proteins **$\alpha_6\beta_4$ integrin** whose intracytoplasmic moieties bind to the **plakin** protein **plectin**, which, in turn, binds to the intermediate filaments **keratin-8** and **keratin-18** (**tonofilaments**).
       - **(a)** The extracellular moieties of $\alpha_6\beta_4$ integrins also bind to the **laminins** and **type IV collagens** of the basal lamina.
       - **(b)** As in type I hemidesmosomes, the intracytoplasmic components form an electron-dense, plaquelike structure that resembles but is different from the outer dense plaque of a desmosome.
   - **b.** Because of their large number of $\alpha_6\beta_4$ integrins and their connection to the tougher intermediate filaments rather than to the less sturdy actin filaments, hemidesmosomes form much stronger anchoring junctions than focal adhesions. However, similar to focal adhesions, the presence of Ca^{2+} ions are necessary for the formation and maintenance of these anchoring junctions and the cell is able to form and disassemble hemidesmosomes as required. Both the

table **3.3** Hemidesmosome Characteristics

Characteristics	Type I Hemidesmosome	Type II Hemidesmosome
Most common locations	Skin, esophagus, oral cavity	Small intestine, large intestine
Transmembrane protein	$\alpha_6\beta_4$ integrin, type XVII collagen (bullous pemphigoid antigen 180)	$\alpha_6\beta_4$ integrin
Intracytoplasmic binding of integrins	Erbin, plectin, bullous pemphigoid antigen 230, and CD151	Plectin
Connection to keratin filaments	Plectin and bullous pemphigoid antigen 230	Plectin
Types of keratin filaments	Keratin-5 and keratin-14	Keratin-8 and keratin-18
Extracellular binding of integrins	Laminin and type IV collagen	Laminin and type IV collagen

formation and disassembly are regulated by a series of intracellular and extracellular signaling events, many of which act during the formation of new cells that either become anchored to the basal lamina or are moving toward the free surface of the epithelium.

c. Keratin filaments (**tonofilaments**) in the cell terminate in the hemidesmosome plaque, allowing these junctions to **link** the cytoskeleton with the components of the extracellular matrix.

CLINICAL CONSIDERATIONS

Bullous pemphigoid, an autoimmune disease in which antibodies are produced against hemidesmosomes, is characterized by chronic generalized **blisters** in the skin, which cause the epidermis to become separated from the underlying connective tissue.

C. Basal plasma membrane infoldings are common in *ion-transporting epithelia* (e.g., distal convoluted tubule of the kidney, striated ducts in salivary glands).

1. They form deep invaginations that compartmentalize mitochondria.

2. Function. They increase the surface area and bring ion pumps (Na^+-K^+ adenosine triphosphatase [ATPase]) in the plasma membrane close to their energy supply (ATP produced in mitochondria).

IV. APICAL EPITHELIAL SURFACES

The apical cell membrane of polarized epithelial cells has an abundance of ion channels, carrier proteins, aquaporins, and a variety of enzymes depending on the functions of the cell. These surfaces may also possess specialized structures such as microvilli, stereocilia, and cilia. Flagella, modified cilia that are present only in spermatozoa, are discussed in Chapter 18.

A. Microvilli are 1-µm long, *glycocalyx*-covered, fingerlike projections of epithelial cell membrane that *extend into a lumen* and increase the cell's surface area, constituting the *brush border* of kidney proximal tubule cells and the *striated border* of intestinal absorptive cells.

1. A bundle of approximately 25 to 30 **actin filaments** runs longitudinally through the core of each microvillus extending from the tip of the microvillus into the **terminal web**, a zone of intersecting filaments in the apical cytoplasm.

a. Actin-binding proteins **villin**, **fimbrin**, **espin**, and **fascin** bind the actin filaments of the bundle to each other; **calmodulin** and **myosin I** secure the peripheral filaments of the actin bundle to the cytoplasmic aspect of the microvillar membrane.

b. The actin filaments are arranged in a specific orientation within the microvillus, so that their **plus ends** (**barbed ends**) extend to the tip of the microvillus where they are embedded in an amorphous material known as **villin**. The **minus ends** (**pointed ends**) of the bundle of actin filaments are affixed to the spectrin and actin components of the terminal web.

2. Myosin II and **tropomyosin** molecules located at the terminal web can interact to contract the apical region of the cell thereby causing the microvilli to diverge from each other, increasing the intermicrovillar spaces providing a larger surface area for an increased transport of materials into and out of the cell.

B. Stereocilia are very *long* (15–20 µm in length) *microvilli* (*they are not cilia*) in the hair cells of the inner ear, in the epididymis, and in the vas deferens of the male reproductive tract. The core of the stereocilia is composed of actin filaments that are attached to each other by **fimbrin** and to the plasmalemma of the stereocilia by **villin-2** and **ezrin** (but not in the hair cells of the inner ear). As in microvilli, the barbed ends of the actin filament bundle extend to the tip of the stereocilia, where villin is absent, and their pointed ends reach and are anchored in the cell web.

C. Cilia are of two types, motile and nonmotile (primary) cilia.

1. The **actively motile cilia** are 7- to 10-µm-long processes of the cell that extend from certain epithelia (e.g., tracheobronchial and oviduct epithelium) that propel substances along the

epithelial surface. Transmission electron microscopy demonstrated that cilia contain a **core** of longitudinally arranged **microtubules** (the **axoneme**), which arises from a **basal body** during ciliogenesis.

a. The **axoneme** (Fig. 3.5) consists of nine doublet microtubules uniformly spaced around two central microtubules (**9 + 2 configuration**), where each doublet microtubule is composed of a complete microtubule, **microtubule A** (composed of 13 protofilaments), and an incomplete microtubule, **microtubule B** (consisting of 10 protofilaments). Microtubule A shares three of its protofilaments with microtubule B so that microtubule B is also a completely closed structure. Each central microtubule consists of 13 protofilaments. Cilia have the following additional components:

(1) Inner and outer ciliary dynein arms extend unidirectionally from one member of each doublet microtubule and interact with adjacent doublets, so that they may slide past one another. The arms consist of **ciliary dynein**, and the head is an **ATPase** that splits ATP to liberate the energy necessary for active movement of a cilium.

(2) Radial spokes extend from each of the nine outer doublets toward the central sheath.

(3) Central sheath surrounds the two central microtubules; it and the radial spokes regulate the ciliary beat.

(4) Nexin, an elastic protein, connects adjacent doublet microtubules to each other and helps to maintain the shape of the cilium.

(5) Tektins are proteins that resemble intermediate filaments and physically support the axoneme by forming linear backbones that attach at the outer aspects (away from the central sheet) of the junction of each microtubule A with its microtubule B.

b. The **basal body** (Fig. 3.5) is a cylindrical structure at the **base of each cilium** that consists of nine triplet microtubules arranged radially in the shape of a pinwheel (**9 + 0 configuration**). It resembles a centriole (Fig. 3.6; also see Fig. 1.8) but has a less complex central organization.

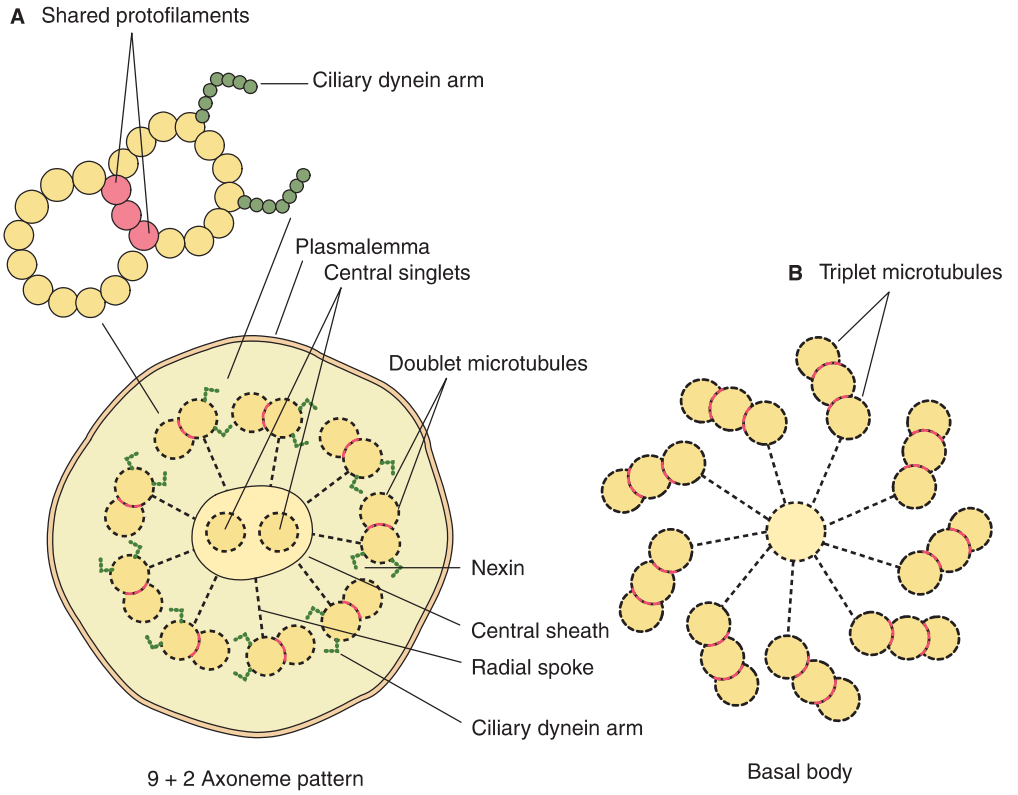


FIGURE 3.5. Cross-sections of a cilium and basal body. (Part A adapted with permission from Junqueira LC, Carneiro J, Kelley RO. *Basic Histology.* 9th ed. Norwalk, CT: Appleton & Lange; 1998:45. Part B adapted with permission from West JB. *Best and Taylor Physiological Basis of Medical Practice.* 12th ed. Baltimore, MD: Williams & Wilkins; 1991:12.)

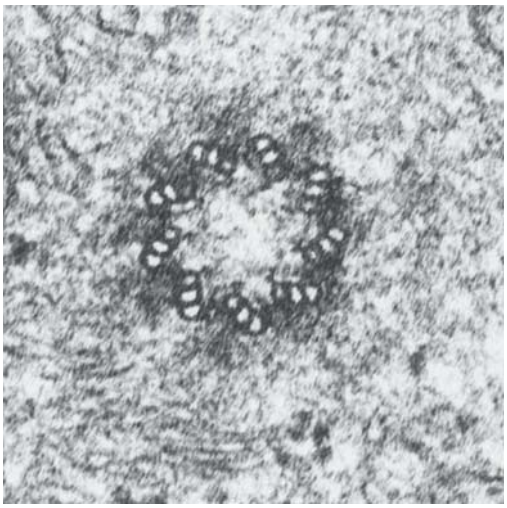


FIGURE 3.6. Electron micrograph of a cross-sectioned centriole. Notice the nine triplet microtubules arranged radially in the shape of a pinwheel. This is known as the 9 + 0 configuration (compare with the cilium), and little central organization is observed.

The inner two triplets of the basal body give rise to the doublet microtubules of the cilium axoneme. The outermost, third microtubule, referred to as **microtubule C**, of the triplet is also incomplete. The region where the basal body and the axoneme merge with each other is frequently referred to as the **transition zone**. The basal body and the structures coupled with it secure the cilium to the cell and also ensure that all cilia of the cell beat in the same direction. Structures that are associated with the basal body are the alar sheet, basal feet, and striated rootlets.

(1) A funnel-shaped fibrous membrane, known as the **alar sheet**, attaches to every microtubule C of the basal body at the transition zone and sweeps upward to merge with the cell membrane at the origin of the cilium. The alar sheet ensures a strong attachment of the basal body to the plasmalemma and is a semipermeable membrane that limits access to the ciliary cytoplasm.

(2) Attached to the basal body is the **basal foot** that probably ensures that all cilia of the same cell are facing in the same direction thereby controlling the synchronous, unidirectional bending of every cilium of the same cell.

(3) Extending from the basal body, and securing it into the cytoplasm, are the protofilaments, known as the **striated rootlets**, which affix the cilium relatively deeply into the apical cytoplasm.

c. Ciliary movement occurs as the dynein arms of a doublet grasp and "climb" along the "back" of the adjacent doublet, thereby bending the cilium in a preferred direction. This is an energy-requiring process and is fueled by the ATPase activity of the head of the dynein arms. As the cilium bends, the elastic proteins of the axoneme become stretched. Once the cilium is bent sufficiently the dynein arms relax their grasp on the adjacent doublet and the cilium snaps back to its original position propelling materials located at its tip thus moving material, such as mucus in the tracheal lumen, along the epithelial surface. The process of "snapping back" does not require energy because it is fueled by the stretched elastic proteins returning to their resting positions.

d. Transport of material occurs within the motile cilia, primary cilia, and flagella, referred to as **axonemal transport**. Within cilia it is known as **intraciliary transport**, and within flagella it is known as **intraflagellar transport**. The transport of tubulin dimers and other molecules required by the cilia occurs via carrier proteins, known as **raft proteins** that pick up cargo, such as tubulin dimers. The raft proteins then become attached to **kinesin** or to **dynein**, motor proteins that ferry cargo along microtubules in an anterograde or retrograde direction, respectively. **Anterograde** is from the basal body toward the tip of the cilium and **retrograde** is in the opposite direction, from the tip of the cilium toward the basal body. To be able to switch from anterograde to retrograde direction, kinesin has to be phosphorylated by the enzyme **intestinal cell kinase** (**ICK**) located at the distal tip of

the cilium. Certain mutated forms of ICK are unable to phosphorylate kinesin, causing a cessation of intraciliary transport.

2. A single **nonmotile cilium** (**primary cilium**) is present on nearly every human cell that is in the G_0 stage of the cell cycle. These structures were believed to be nonfunctional evolutionary remnants, but recently it has been demonstrated that they have essential functions in the organization of signaling pathways not only during embryonic development but also in the adult organism. It has been amply demonstrated that impaired primary cilia are responsible for various anomalous conditions, known as **ciliopathies**.
   - **a.** The axoneme of primary cilia differ from those of motile cilia in that they possess no central singlets; thus, they have a **9 + 0 configuration**; moreover, the central sheet, outer and inner dynein arms, and most radial spokes are absent.
   - **b.** A set of proteins, known as **BBSome** (named after Bardet–Biedl syndrome), is located at the distal end of the basal body and is responsible for the formation as well as the proper functioning of the primary cilium. This BBSome protein complex determines which molecules are permitted entry into the cytoplasm of the primary cilium. Disruption of the BBSome is responsible for a number of ciliopathies, including Bardet–Biedl syndrome.
   - **c.** If a cell leaves the G_0 stage of the cell cycle and enters the G_1 phase, the primary cilium becomes resorbed and the **basal body** returns to its previous function as a centriole.
   - **d.** Primary cilia of a particular region, such as the kidney tubule or fibroblasts, are oriented in the same direction and this precise alignment is dictated by the **basal foot**. This precise alignment permits the primary cilia to perform their functions whether in the monitoring of the flow of the ultrafiltrate in the kidney tubule or in the migration of fibroblasts in the proper direction during wound healing.
   - **e.** A number of ion channels and select receptors are known to be present only in the membranes of primary cilia. The specific reason for this exclusivity has not been elucidated, but it may have some association with the **intraciliary transport mechanism**, and disturbances of this particular cellular event are responsible for the various **ciliopathies**.

CLINICAL CONSIDERATIONS

Immotile cilia syndrome (**primary ciliary dyskinesia**) results from a genetic defect that causes an abnormal ciliary beat or the absence of a beat. In this syndrome, cilia have axonemes that lack ciliary dynein arms and have other abnormalities. The syndrome is associated with recurrent lower respiratory tract infections, reduced fertility in women, and sterility in men.

Another form **of immotile cilia syndrome** results from a genetic defect that causes the absence of the central pair of microtubules. These cilia of the ependymal cells lining the ventricles of the brain are unable to beat, resulting in the disturbance of the normal movement of the cerebrospinal fluid (CSF) causing an excess accumulation of the CSF producing a condition known as **hydrocephalus**.

Autosomal dominant polycystic kidney disease is a genetic disorder that occurs in about 2 per 1,000 births. Three mutations are responsible for this anomaly, namely PKD-1, PKD-2, and PKHD-1, but most cases are due to mutations in gene *PKD-1* located on chromosome 16 (where PKD = polycystic kidney disease gene). For an unknown reason, individuals with these mutations develop abnormal primary centrioles resulting in abnormal cell cycles as well as defective calcium transport within the cell. During embryonic development, cysts begin forming on the kidneys that increase in size and number. As they continue to gain fluid and become larger, they apply pressure on the uriniferous tubules and prevent them from performing their function. In most patients, the symptoms, such as pain in the back and sides as well as headaches, become evident by the 40th year of life. Eventually, patients' kidney function is reduced until they have to be placed on renal dialysis and become eligible for kidney transplant.

Bardet–Biedl syndrome is a disorder caused by disruptions in the normal functioning of BBSome located at the base of the basal body of the primary cilium. The manifestations of this syndrome are varied and include night blindness, speech disorder, malformations of the rods and cones of the retina with a subsequent loss of vision, presence of extra digits on the hands and feet, kidney failure, urogenital defects, and obesity. Many patients succumb to kidney failure.

V. GLANDS

Glands arise from an epithelium that penetrates the connective tissue and forms secretory units.

A. Structure. A gland consists of a functional portion (**parenchyma**) of secretory and ductal epithelial cells, which is separated by a basal lamina from supporting connective tissue elements (**stroma**).

B. Classification. Glands are classified into three types based on the site of secretion. **Exocrine glands** secrete into a duct or onto a surface. **Endocrine glands** secrete into the bloodstream. **Paracrine glands** secrete into the local extracellular space.

1. **Exocrine glands**
   a. **Unicellular glands** are composed of a single cell (e.g., goblet cells in tracheal epithelium).
   b. **Multicellular glands (Fig. 3.7)**
      (1) Classification is based on two criteria.
         (a) Multicellular glands are classified according to **duct branching** as **simple glands** (duct does not branch) or **compound glands** (duct branches).

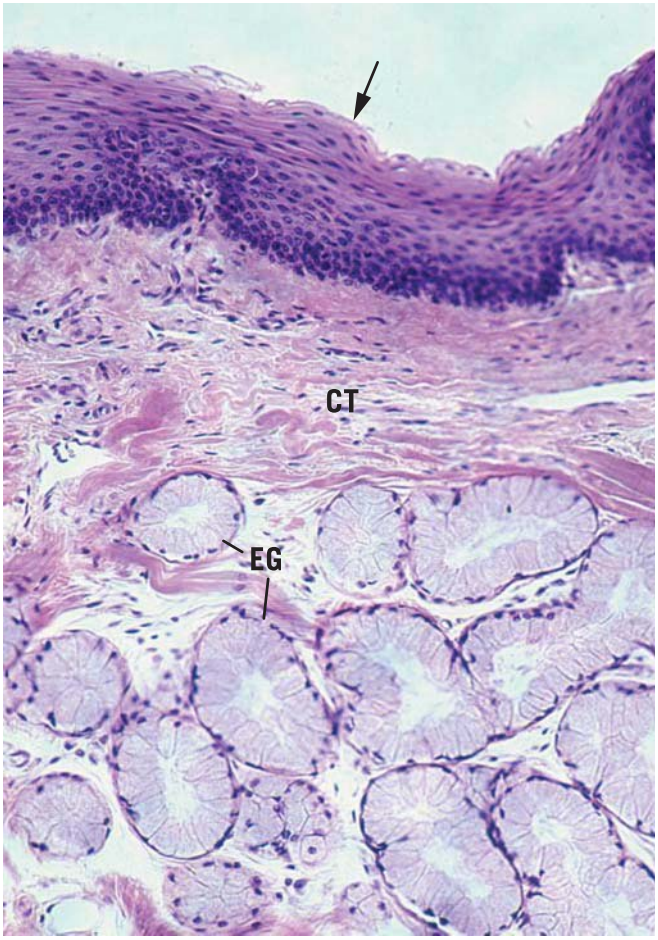


FIGURE 3.7. Light micrograph showing stratified squamous nonkeratinized epithelium (*arrow*) lining the lumen of the esophagus. This epithelium is thick, and cells in its upper layers are flattened or squamous, whereas the basal cells that undergo mitosis and give rise to cells of the upper layer are cuboidal. Esophageal cardiac glands (EG) are present in the connective tissue (CT) layer (lamina propria) deep to the epithelium. These glands are located in the vicinity of the esophageocardiac junction, and they are lined by simple columnar epithelial cells that secrete mucus.

(b) They are further classified according to the **shape of the secretory unit** as **acinar** (sac-like) or **tubular** (straight, coiled, or branched); tubuloacinar (mixed); or, occasionally, **alveolar** (flasklike).

(2) A connective tissue capsule may surround the gland, or septa of connective tissue may divide the gland into **lobes** and smaller **lobules**.

(3) Glands may have **ducts** between lobes (**interlobar**), within lobes (**intralobar**), between lobules (**interlobular**), or within lobules (**intralobular**), such as striated and intercalated ducts.

(4) Multicellular glands secrete various substances.

(a) *Mucus* is a viscous material that usually protects or lubricates cell surfaces.

(b) *Serous* secretions are watery and often rich in enzymes.

(c) *Mixed* secretions contain both mucous and serous components.

(5) Mechanisms of secretion vary.

(a) In **merocrine** glands (e.g., parotid gland), the secretory cells release their contents by exocytosis.

(b) In **apocrine** glands (e.g., lactating mammary gland), part of the apical cytoplasm of the secretory cell is released along with the contents.

(c) In **holocrine** glands (e.g., sebaceous gland), the entire secretory cell along with its contents is released.

2. **Endocrine glands** may be **unicellular** (e.g., individual endocrine cells in gastrointestinal and respiratory epithelia) or **multicellular** (e.g., adrenal gland), and they **lack a duct system**. In multicellular glands, secretory material is released into fenestrated capillaries, which are abundant just outside the basal lamina of the glandular epithelium.

CLINICAL CONSIDERATIONS

Epithelia sometimes undergo **metaplasia** in response to persistent injury. Metaplasia is the conversion of one type of differentiated epithelium into another. Most commonly, a glandular epithelium is transformed into a squamous epithelium. However, in cases of chronic acid reflux from the stomach into the lower esophagus, the stratified squamous nonkeratinized epithelium is replaced by a glandular mucus-secreting epithelium (**Barrett epithelium**) similar to that found lining the cardia of the stomach. This helps to protect the esophagus against the injurious effects of the acid and pepsin, and is also a well-known precursor of esophageal adenocarcinoma.

Epithelial cell tumors occur when cells fail to respond to normal growth regulatory mechanisms. Such tumors are **benign** when they remain **local** and they are **malignant** when they **invade neighboring tissues**. They may (or may not) **metastasize** to other parts of the body. **Carcinomas** are malignant tumors that arise from **surface epithelia. Adenocarcinomas** are malignant tumors that arise from **glands.**

Review Test

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A male medical student is married with a child from his wife's previous marriage. They have been trying to have a child in common for several years but have been unable to do so. They seek the advice of a fertility specialist who asks the husband if he has chronic lower respiratory infections. When the husband replied in the affirmative, the physician supposes that the husband may be sterile and suggests a series of tests. What does the physician suspect?

(A) Low testosterone levels
(B) Blockage of the seminiferous tubules
(C) Primary ciliary dyskinesia
(D) Bilateral cryptorchidism
(E) Low sperm count

2. A medical student who volunteers in an immunochemistry laboratory suspects that she may have antibodies produced against type XVII collagen. She tested her blood and found that she did indeed have type XVII collagen antibodies. Which of the following symptoms made her suspect the presence of these antibodies?

(A) She has patches of dark skin with brittle, corkscrew-shaped hair.
(B) She has widespread blistering of her skin.
(C) Her skin is hot to the touch.
(D) She has constant itching sensations.
(E) She has a large numbers of petechiae.

3. A patient has a malignant tumor arising from glandular epithelium. What is the proper category for such a tumor?

(A) Adenocarcinoma
(B) Sarcoma
(C) Carcinoma
(D) Metaplasia
(E) Barrett epithelium

4. Which of the following is a condition affecting the epidermis of the skin in which blisters do not form?

(A) Adenocarcinoma
(B) Bullous pemphigoid
(C) Carcinoma
(D) First-degree burn
(E) Sarcoma

The next two questions are based on the following scenario:

A 13-year-old boy is seen by his pediatrician because he started to have problems with tripping and stumbling. He also lost muscle bulk and muscle strength in his lower legs. Around the same time, he developed an unusual gait in which he lifts his foot much higher than normal.

5. What is the most probable diagnosis?

(A) Malnutrition
(B) Charcot–Marie–Tooth disease
(C) Osteopenia
(D) Osteoporosis
(E) Early onset osteoarthritis

6. What is the underlying cause of the boy's condition?

(A) Anomalous zonulae occludentes
(B) Anomalous hemidesmosomes
(C) Anomalous zonulae adherentes
(D) Anomalous gap junctions
(E) Anomalous desmosomes

The next two questions are based on the following scenario:

A 44-year-old male has been complaining for the past 4 years of backache, headache, and pain in the side that has been increasing in intensity. Additionally, his blood pressure has become elevated, and he has started having pain in his abdominal region. He came to see his physician because of blood in his urine and pain on urination.

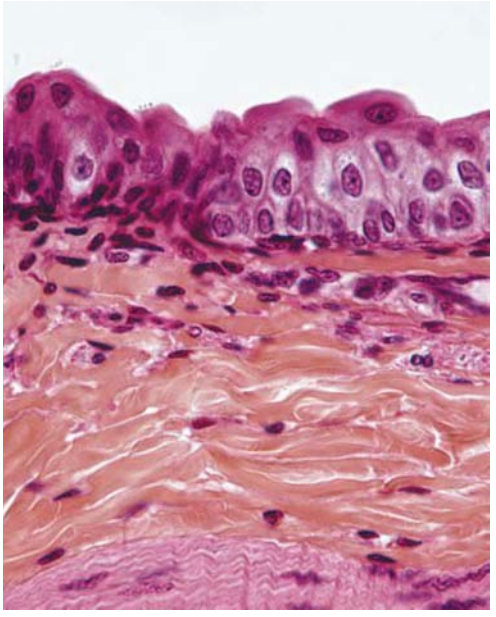
7. What is the most probable diagnosis?

(A) Kidney stones
(B) Urinary tract infection
(C) Benign prostatic hypertrophy
(D) Prostatic cancer
(E) Polycystic kidney disease

8. What is the underlying cause of this patient's condition?

(A) Abnormal primary cilia
(B) Abnormal motile cilia
(C) Bacterial infection
(D) Diet high in calcium
(E) Abnormal microvilli

Question 9 refers to the photomicrograph below.



9. The photomicrograph presents the healthy region of a biopsy of a cancerous lesion. This patient has cancer of the

(A) urinary bladder.
(B) gallbladder.
(C) esophagus.
(D) soft palate.
(E) hard palate.

10. Which one of the following statements about the gap junction is true?

(A) It extends as a zone around the apical perimeter of adjacent cells.
(B) It possesses dense plaques composed in part of desmoplakins.
(C) It permits the passage of ions from one cell to an adjacent cell.
(D) Its adhesion depends on calcium ions.
(E) It possesses transmembrane linker glycoproteins.

Answers and Explanations

1. **C.** Individuals with primary ciliary dyskinesia commonly have recurrent respiratory infections if the cilia are unable to clear the respiratory epithelium of microorganisms, debris, and so forth. Examination of the student's ejaculate probably show that he has viable but nonmotile spermatozoa, which is caused by a genetic defect resulting in cilia with axonemes that lack ciliary dynein arms and thus are unable to beat.
2. **B.** She has widespread blistering of her skin and suspected that she is suffering from bullous pemphigoid, an autoimmune disease in which she formed antibodies against her own type XVII collagen, one of the transmembrane proteins of their hemidesmosomes.
3. **A.** Adenocarcinomas are epithelial tumors that originate in glandular epithelia. Carcinomas originate from surface epithelia. Sarcomas arise from connective tissue. Metaplasia is the conversion of one type of epithelium to another. Barrett epithelium is the replacement of the esophageal epithelium by a glandular epithelium.
4. **D.** First-degree burns damage the upper layers of the epidermis only, and blisters do not form in the skin.
5. **B.** Charcot–Marie–Tooth disease usually begins manifesting in early adolescence with problems of walking and change in the individual's gait. Muscle mass is gradually lost in the lower limb.
6. **D.** A mutation in the gene coding for the protein connexin (Cx32) of myelin results in the degeneration of the myelin sheath of the peripheral nerves supplying muscles of the limbs; consequently, the muscles served by these nerves begin to atrophy.
7. **E.** The combination of symptoms suggested to the physician that the patient is suffering from polycystic kidney disease.
8. **A.** The underlying cause of this patient's condition is a mutation in the PKD-1 gene located on chromosome 16 that is responsible for the abnormal primary cilia. This mutation results in the continued development of cysts on the kidney causing eventual kidney failure.
9. **A.** The patient has urinary bladder cancer because the epithelial lining in the photomicrograph is transitional epithelium.
10. **C.** The gap junction channel regulates the passage of ions and small molecules from cell to cell, excluding those having a molecular weight greater than 1,200 Da. The tight junction is the zone of adhesion around the apical perimeter of adjacent cells. The other statements are characteristics of desmosomes.

chapter 4

Connective Tissue

I. OVERVIEW—CONNECTIVE TISSUE

Connective tissue is formed primarily of **extracellular matrix** (ECM; see Chapter 2), consisting of **ground substance** and **fibers**, in which various connective tissue **cells** are embedded. It **supports** organs and cells, acts as a **medium for exchange** of nutrients and wastes between the blood and tissues, **protects** against microorganisms and other pathogens, mounts immune responses, **repairs** damaged tissues, and **stores fat**. The various categories of connective tissue include connective tissue proper, the subject of this chapter; blood, discussed in Chapter 5; and cartilage and bone, discussed in Chapter 6.

II. CONNECTIVE TISSUE CELLS

Cells of connective tissue may originate locally and remain in the connective tissue (**fixed cells**) or originate elsewhere and remain only temporarily in the connective tissue compartment (**transient cells**) (Fig. 4.1). **Fixed connective tissue cells** include fibroblasts, pericytes, adipose cells, mast cells, and fixed macrophages. **Transient connective tissue cells** include certain macrophages, lymphocytes, plasma cells, neutrophils, eosinophils, and basophils.

A. Fixed cells (Table 4.1)

1. **Fibroblasts**, the predominant cells in connective tissue proper (Fig. 4.2), arise from mesenchymal cells of the embryo. Fibroblasts often possess an oval nucleus with two or more nucleoli; they seldom undergo mitosis except in wound healing, and, under certain conditions, may differentiate into other cell types. They are responsible for manufacturing almost the entire ECM and, when actively synthesizing ECM, they are spindle shaped (fusiform), house a well-developed rough endoplasmic reticulum (RER) and many Golgi complexes, and are referred to as **active fibroblasts**. Myosin is located throughout the cytoplasm, and actin and α-actinin are located at the cell periphery. Inactive fibroblasts are frequently called fibrocytes.

CLINICAL CONSIDERATIONS

Fibroblasts undergo mitosis only during wound healing. However, under certain conditions, fibroblasts may differentiate into adipose cells, or, during fibrocartilage formation, they may differentiate into chondrocytes. In addition, under severe pathologic conditions, fibroblasts may differentiate into osteoblasts.

2. **Pericytes** (**adventitial cells**; **perivascular cells**) are associated with capillaries, sharing their basement membranes. They are also embryonic mesenchymal cell derivatives and may retain a **pluripotential capacity**.

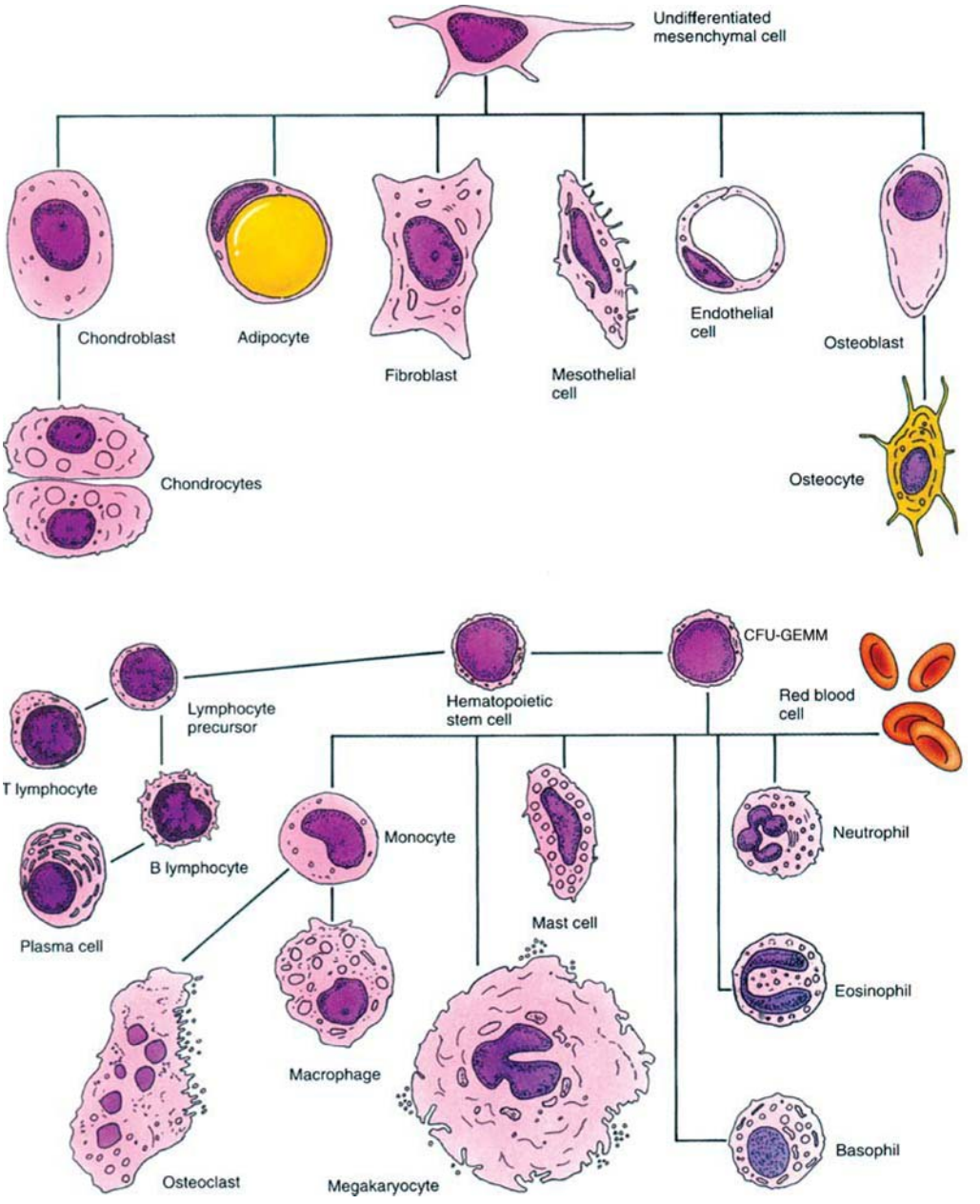


FIGURE 4.1. Origin of connective tissue cells. Cells arising from undifferentiated mesenchymal cells are formed in connective tissue and remain there. Cells arising from hematopoietic stem cells are formed in the bone marrow and reside transiently in connective tissue. (Reprinted with permission from Gartner LP. *Textbook of Histology*. 4th ed. Philadelphia, PA: Elsevier; 2017:128.)

a. Pericytes have characteristics of endothelial cells as well as of smooth muscle cells because they contain actin, myosin, and tropomyosin; their contractile abilities assist in influencing blood flow through capillaries.

b. During blood vessel formation and repair, pericytes may differentiate into fibroblasts, smooth muscle cells, as well as endothelial cells of blood vessel walls.

3. **Adipose cells** (**adipocytes**) (Figs. 4.1 and 4.3) arise from mesenchymal cells and perhaps from fibroblasts. Adipogenesis occurs pre- and postnatally, but adipocytes do not normally undergo cell division beyond age 2 years. However, in morbidly obese individuals, the cells not only

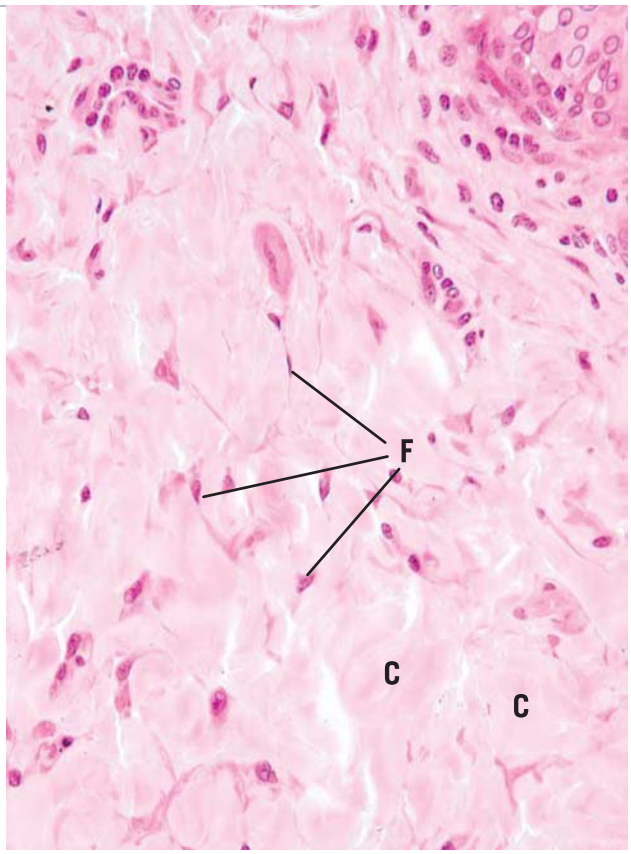


FIGURE 4.2. Light micrograph of monkey bladder (×270) illustrating fibroblasts (F) and collagen bundles (C) within the connective tissue.

become enlarged but also form new fat cells. Adipocytes are surrounded by a basal lamina and are responsible for the **synthesis**, **storage**, and **release of fat** as well as for releasing **hormones**. The two types of fat cells are unilocular and multilocular.

- **a. Unilocular adipose cells**, surrounded by a basal lamina, contain a single large fat droplet that squeezes the cytoplasm and nucleus into a thin rim around the cell's periphery. They synthesize, store, and release fat.
  - **(1)** These cells have plasmalemma **receptors** for insulin, growth hormone, norepinephrine, and glucocorticoids to **control the uptake and release of free fatty acids and triglycerides**.
- **b. Multilocular adipose cells**, smaller than unilocular adipose cells, store their fat in many small droplets; their spherical nucleus is centrally located. As described below, they function in the generation of heat.

4. Mast cells (Fig. 4.1) arise from myeloid stem cells in bone marrow and usually reside near small blood vessels. They are similar to basophils but develop from different precursors and thus are not related.

- **a.** These cells are among the largest cells of connective tissue proper. They possess a central spherical nucleus; their cytoplasm is filled with coarse, deeply stained metachromatic granules; their contents (known as **primary mediators**) are listed in Table 4.1.
- **b.** Mast cell surfaces are folded; in transmission electron micrographs they display a well-developed Golgi complex, scant RER, and many dense lamellated granules.
- **c.** Two populations of mast cells exist: **connective tissue mast cells** possess secretory granules containing heparin whereas the smaller **mucosal mast cells**, located in the mucosa of the alimentary canal and of the respiratory tract, contain chondroitin sulfate in their secretory granules. The central nervous system (CNS) does not contain mast cells, presumably to prevent the possibility of an inflammatory response.

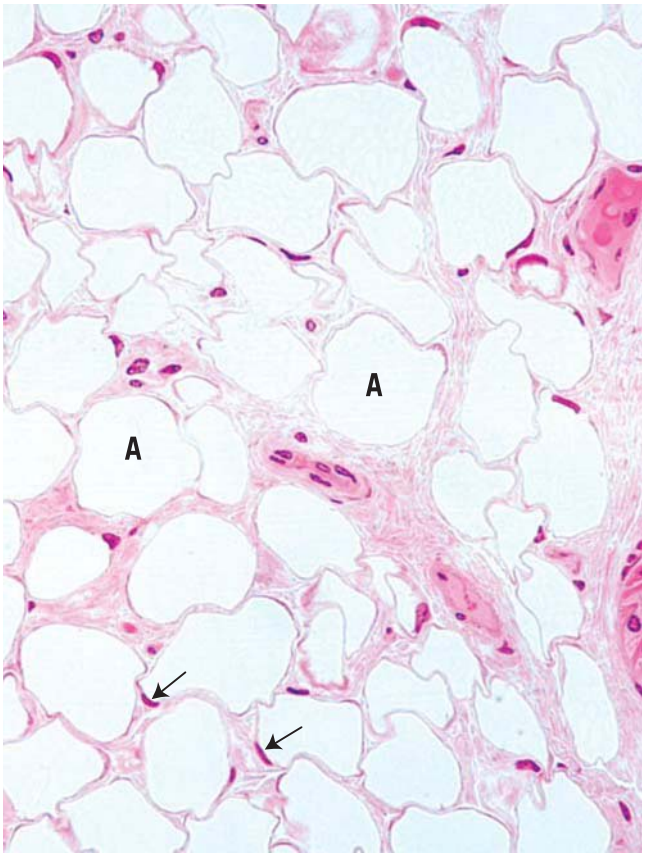


FIGURE 4.3. Light micrograph of monkey skin (×270). Observe the fat cells (adipocytes, A) and their nuclei (*arrows*) that have been displaced to the periphery of the cell. Note that the fat was extracted during processing.

table **4.1** Major Mediators Released by Mast Cells

Substance	Intracellular source	Action
Primary mediators		
Histamine	Granules	Vasodilator; increases vascular permeability, causes contraction of bronchial smooth muscle; increases mucus production
Heparin	Granules	Anticoagulant; inactivates histamine
Eosinophil chemotactic factor	Granules	Attractant for eosinophils to site of inflammation
Neutrophil chemotactic factor	Granules	Attractant for neutrophils to site of inflammation
Aryl sulfate	Granules	Inactivates leukotriene C_4, limiting inflammatory response
Chondroitin sulfate	Granules	Binds and inactivates histamine
Neutral proteases	Granules	Protein cleavage to activate complement; increases inflammatory response
Secondary mediators		
Prostaglandin D_2	Membrane lipid	Causes contraction of bronchial smooth muscle; increases mucus secretion; vasoconstriction
Leukotrienes C_4, D_4, E_4	Membrane lipid	Vasodilators; increases vascular permeability; contraction of bronchial smooth muscle
Bradykinins	Membrane lipid	Causes vascular permeability; responsible for pain sensation
Thromboxane A_2	Membrane lipid	Causes platelet aggregation; vasoconstriction
Platelet-activating factor	Activated by phospholipase A_2	Attracts neutrophils and eosinophils; causes vascular permeability; contraction of bronchial smooth muscle

d. When mast cells become activated during a type I hypersensitivity reaction, phospholipids of their cell membranes can be converted into **arachidonic acid** by the enzyme **phospholipase A_2**. Arachidonic acid is, in turn, converted into **secondary mediators** (e.g., leukotrienes and prostaglandins; Table 4.1).

e. Mast cells mediate **immediate** (**type I**) **hypersensitivity** reactions (**anaphylactic reactions**) as follows:

(1) When an individual is exposed to a specific **allergen** (such as pollens, insect venoms, and foreign serum) for the *first time,* the person's plasma cells manufacture **immunoglobulin E** (**IgE**). These antibodies bind to **FcεRI receptors** on the surface of mast cells and basophils, causing these cells to become **sensitized**.

(2) During a *second exposure* to the same allergen, the allergen binds to the membrane-bound IgE, leading to cross-linking and clustering of the **allergen–IgE complexes**, which trigger the release of primary and secondary mediators by the mast cell (Fig. 4.4 and Table 4.2 detail the consequences; also see Chapter 10).

5. Macrophages (Fig. 4.1) are considered to be both fixed and transient. They are described in the transient cell category.

a. In the past, certain cells were named without realizing that they were macrophages located in various regions of the body (e.g., Kupffer cells in the liver; dust cells in the lungs; osteoclasts in bone; Langerhans cells in skin; microglia in CNS). Their specialized names have been retained for historical reasons.

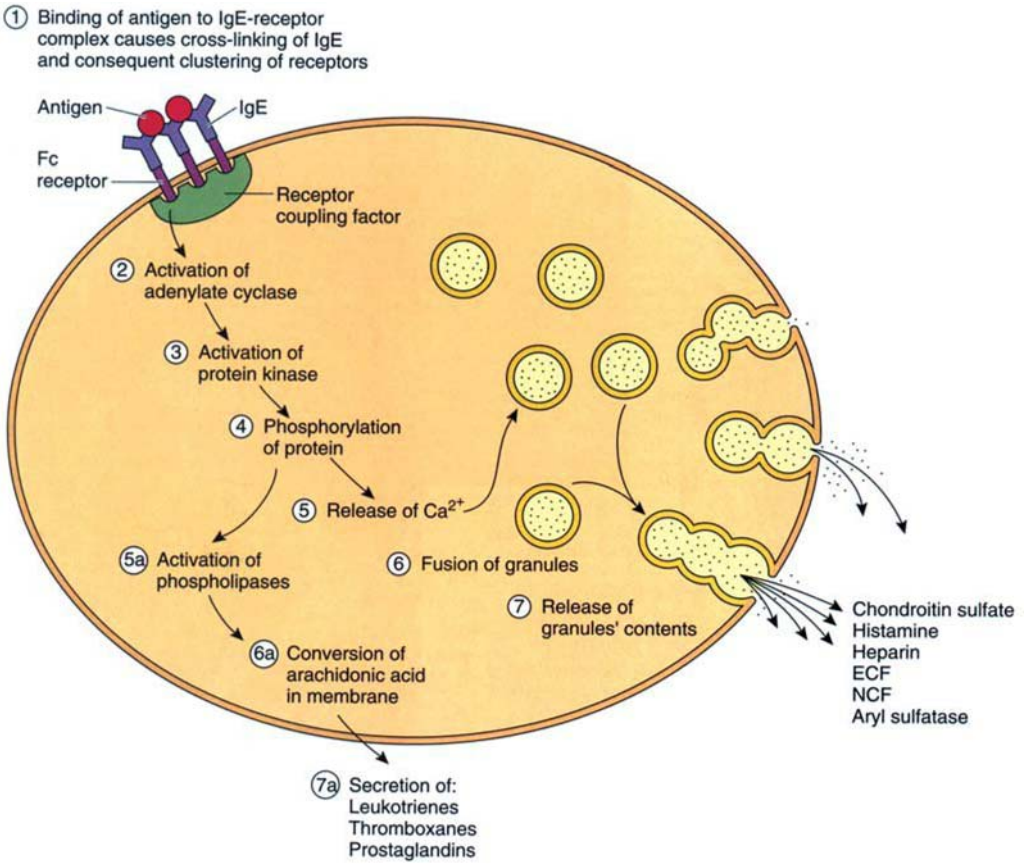


FIGURE 4.4. Activation and degranulation of the mast cell. ECF, eosinophil chemotactic factor; NCF, neutrophil chemotactic factor. (Adapted with permission from Gartner LP. *Textbook of Histology.* 4th ed. Philadelphia, PA: Elsevier; 2017:135.)

table 4.2 Connective Tissue Proper Cells

Cell	Type	Function
Fibroblasts	Fixed	Manufactures almost all of the extracellular matrix
Pericytes	Fixed	Have pluripotential capacity; contractile ability regulates blood flow through capillaries
Unilocular adipose cells	Fixed	Synthesize, store, and release fat; have endocrine function
Multilocular adipose cells	Fixed	Uncouple oxidation from phosphorylation releasing heat
Mast cells	Fixed	Initiate and control inflammatory process
Macrophages	Fixed and transient	Phagocytosis as well as antigen presenting, thus participating in immune reactions
Lymphoid cells	Transient	Function in the immune process
Plasma cells	Transient	Manufacture immunoglobulins (antibodies)
Neutrophils	Transient	Phagocytose and kill bacteria
Eosinophils	Transient	Kill parasites; phagocytose antibody–antigen complexes
Basophils	Transient	Initiate and control inflammatory process

CLINICAL CONSIDERATIONS

Hay fever is characterized by nasal congestion caused by localized edema in the nasal mucosa. This edema results from the increased permeability of small blood vessels because of excessive release of histamine from mast cells in the nasal mucosa.

People with **asthma** have difficulty breathing caused by bronchospasms resulting from **leukotrienes** released in the lungs.

Anaphylactic shock, an extreme case of such reaction in hyperallergic individuals, results from the effects of powerful mediators released during an **immediate hypersensitivity reaction** following a second exposure to an allergen with, if untreated, possibly lethal consequences. This reaction can become systemic and can occur within seconds or minutes after contact with an allergen. Signs and symptoms include shortness of breath; decreasing blood pressure; and other, more serious, signs and symptoms of shock.

B. Transient cells (Table 4.2)

1. **Macrophages** (Fig. 4.1) are the principal **phagocytes** of connective tissue proper.
   - **a.** Macrophages originate in the bone marrow as **monocytes**, circulate in the bloodstream, and then migrate into the connective tissue, where they develop into functional macrophages. Macrophages increase in number because of the activity of the macrophage colony-stimulating factor (M-CSF). Another factor, the colony-forming unit monocyte (CFU-M), facilitates the mitosis and differentiation of monocytes to form macrophages.
   - **b.** Macrophages are members of the **mononuclear phagocyte system**. They are **antigen-presenting cells**, in that they phagocytose antigens; break them down into epitopes; and, using major histocompatibility complex (MHC) I or MHC II molecules, place the epitopes on their cell surface to present it to immunocompetent T cells (see Chapter 10).
   - **c.** Macrophages display FcεRI receptors as well as receptors for complement.
   - **d.** When activated, they display filopodia, an eccentric kidney-shaped nucleus, phagocytic vacuoles, lysosomes, and residual bodies.
   - **e.** Macrophages are responsible for destroying large foreign particulate matter invading connective tissue proper and assisting in the **immune response**. They also secrete substances that function in wound healing.
   - **f.** When stimulated, they may fuse to form **foreign body giant cells**, multinucleated cells that surround and phagocytose large foreign bodies.
2. **Lymphoid cells** (Fig. 4.1) arise from lymphoid stem cells during hemopoiesis (see Chapter 5) and are located throughout the body in the subepithelial connective tissue compartments where they form clusters of cells specialized in mounting an immune response. Generally speaking,
   - **a.** **T lymphocytes** (**T cells**) initiate the **cell-mediated immune response**.
   - **b.** **B lymphocytes** (**B cells**) differentiate into **plasma cells**, which manufacture antibodies and function in the **humoral immune response**.

c. **Natural killer cells** (**NK cells**) lack the surface determinants characteristic of T and B lymphocytes but may display **cytotoxic activity** against tumor cells.

3. **Plasma cells** (Fig. 4.1) are **antibody-manufacturing cells** that arise from activated B lymphocytes and are responsible for **humoral immunity**.
   a. These ovoid cells contain an eccentric nucleus possessing **clumps of heterochromatin**, which appear to be arranged in a spoke-wheel/clock-face fashion.
   b. The abundance of RER is responsible for their deeply basophilic cytoplasm.
   c. A prominent area adjacent to the nucleus appears pale and contains the Golgi complex (negative Golgi image).
   d. They are most abundant at wound entry sites or in areas of chronic inflammation.
4. **Granulocytes** (Fig. 4.1) are white blood cells that possess cytoplasmic granules and arise from myeloid stem cells during hemopoiesis. At sites of inflammation, they leave the bloodstream and enter the loose connective tissue, where they perform their specific functions (see Chapter 5).
   a. **Neutrophils phagocytose**, **kill**, and **digest bacteria** at sites of acute inflammation. **Pus** is an accumulation of dead neutrophils, dead bacteria, extracellular fluid, and additional debris.
   b. **Eosinophils** bind to antigen–antibody complexes on the surface of parasites (e.g., helminths) and then release cytotoxins that damage the parasites.
      (1) They are most prevalent at sites of chronic or allergic inflammation where they phagocytose **antibody–antigen complexes**.
      (2) Eosinophils follow an increasing gradient of eosinophil chemotactic factor, secreted by mast cells and basophils, at sites of allergic inflammation. Having reached those sites, eosinophils release enzymes that cleave histamine and leukotriene C, thus **moderating the allergic reaction**.
   c. **Basophils** are similar to mast cells in that they possess FcεRI receptors, their granules house the same primary mediators, and the same secondary mediators are manufactured de novo from the phospholipids of their plasmalemma. They differ, however, in that they circulate via the bloodstream, whereas mast cells do not.

III. CONNECTIVE TISSUE CLASSIFICATION

Classification is based on the proportion of cells to fibers and on the arrangement and type of fibers (embryonic connective tissue, connective tissue proper, or specialized connective tissue).

A. Embryonic connective tissue

1. **Mucous tissue** (**Wharton jelly**) consists of a jelly-like matrix in which some collagen fibers and large, stellate fibroblasts are embedded.
2. **Mesenchymal tissue** (Fig. 4.5), present almost exclusively in embryos, consists of a gel-like amorphous matrix containing only a few scattered reticular fibers, in which star-shaped, pale-staining mesenchymal cells are embedded. Mitotic figures are often observed in these pluripotent cells.

B. Connective tissue proper

1. **Loose** (**areolar**) **connective tissue** is well vascularized, flexible, and not very resistant to stress; it possesses fewer fibers but more cells and is more abundant than dense connective tissue. Along with adipose tissue, it is the predominant connective tissue of the hypodermis.

CLINICAL CONSIDERATIONS

Edema is a pathologic process resulting in an **increased volume of extracellular fluid**. It may be caused by venous obstruction or decreased venous blood flow (as in congestive heart failure), increased capillary permeability (because of injury), starvation, excessive release of histamine, and obstruction of lymphatic vessels. Edema that is responsive to localized pressure (i.e., depressions persist after release of pressure) is called **pitting edema**.

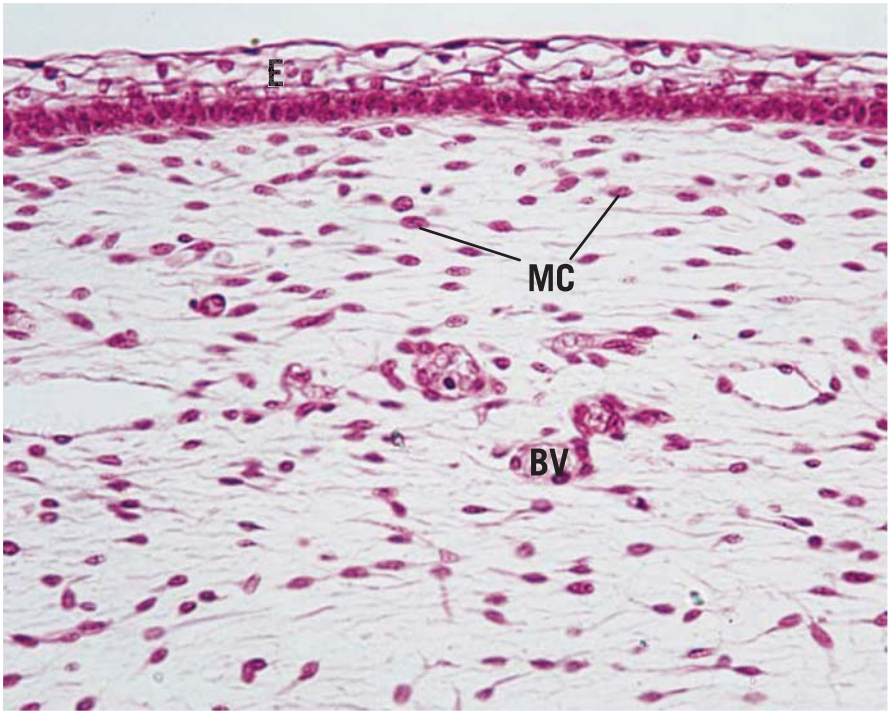


FIGURE 4.5. This is a photomicrograph of a pig embryo. Note that the epithelium (E) overlies the embryonic connective tissue rich in mesenchymal cells (MCs). BV, blood vessel.

2. **Dense connective tissue** contains more fibers but fewer cells than loose connective tissue. It is classified by the orientation of its fiber bundles into two types:
   a. **Dense irregular connective tissue**, whose type I collagen fiber bundles have no definite orientation, is characteristic of the **dermis** and **capsules of many organs**.
   b. **Dense regular connective tissue** contains type I collagen fiber bundles and attenuated fibroblasts that are arranged in a uniform parallel fashion. This tissue may be collagenous (tendons and ligaments) or elastic (ligamentum nuchae, ligamentum flava).
3. **Elastic tissue** is composed of coarse, branching elastic fibers (composed of elastin and fibrillin) with a sparse network of collagen fibers and some fibroblasts filling the interstitial spaces. It is present in the dermis, lungs, elastic cartilage, and elastic ligaments and in large (conducting) blood vessels, where it forms fenestrated sheaths.
4. **Reticular tissue** consists mostly of a network of branched reticular fibers (**type III collagen**) (Fig. 4.6). It invests liver sinusoids, smooth muscle cells, and fat cells and forms the stroma of lymphatic organs, bone marrow, and endocrine glands and also forms the reticular lamina of basement membranes.
5. **Adipose tissue** (Fig. 4.7) has three types of adipocytes: white, beige (brownlike; brite), and brown. White adipose cells have a rich neurovascular supply; store fat (triglycerides); and as a tissue, insulates and cushions the body and acts as a shock absorber. Insulin and prostaglandins assist in the control of lipid storage in white adipose cells. Brown adipose cells generate heat and beige adipocytes can also generate heat under specific circumstances.
   a. **White adipose tissue** is composed of **unilocular** adipose cells and constitutes nearly all of the adult adipose tissue throughout the body. It controls the body's fatty acid homeostasis by accumulating free fatty acids during an excess of caloric ingestion and releasing free fatty acids during a scarcity of caloric intake.
      (1) White adipose tissue **stores and releases lipids** as follows:
         (a) The enzyme **lipoprotein lipase**, synthesized by adipocytes, is transferred to the luminal aspect of the capillary endothelium.

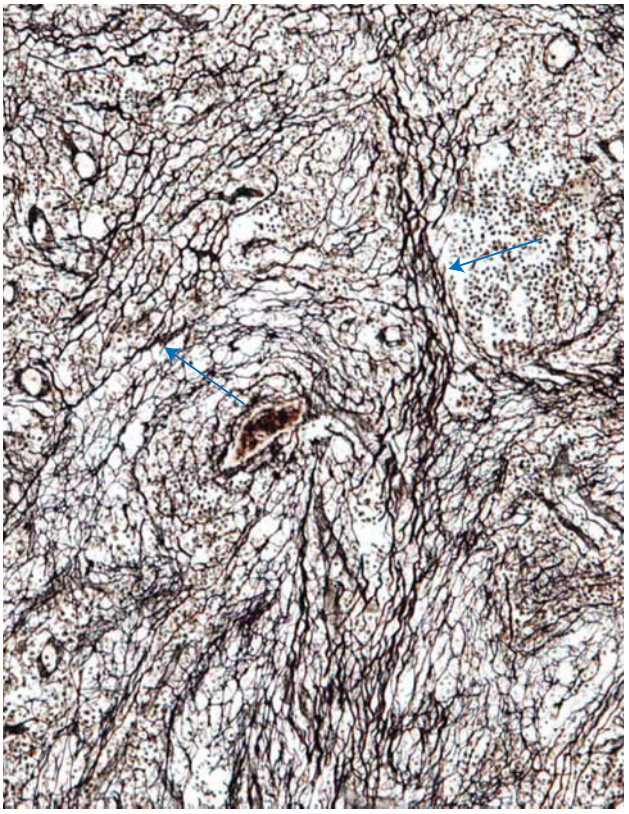


FIGURE 4.6. Light micrograph of reticular tissue (silver stain) (×132). Observe the reticular fibers at the tips of the *arrows*.

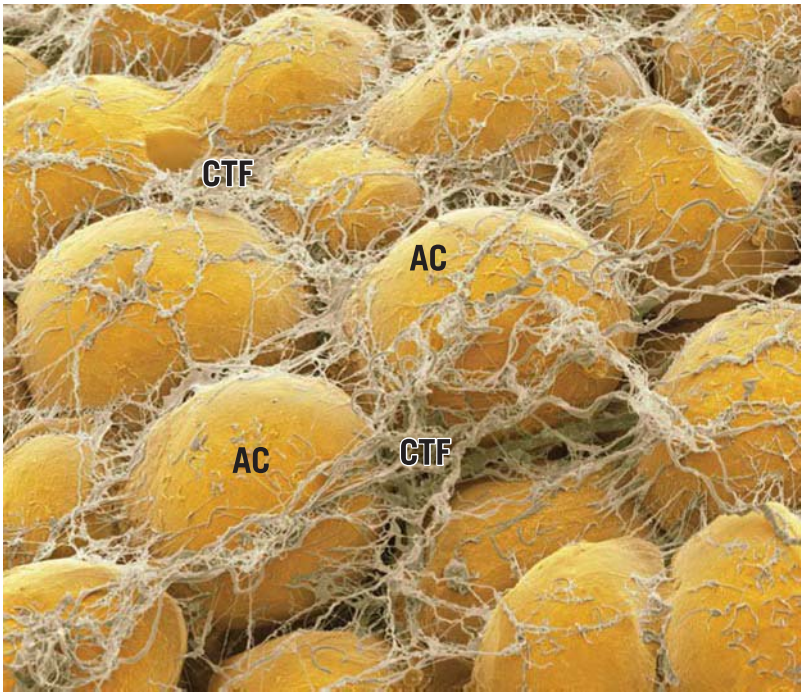


FIGURE 4.7. This is an artificially colored scanning electron micrograph of white adipose tissue. Note the large, adipose cells (ACs) surrounded by connective tissue fibers (CTFs). (Courtesy of Steve Gschmeissner/Science Source.)

(b) **Very low density lipoproteins** and **chylomicrons** are transported in the vascular supply to capillaries of adipose tissue where they are hydrolyzed by lipoprotein lipase into **free fatty acids** and **glycerol**. These cross the cell membrane to enter the adipocyte cytoplasm where they are re-esterified and stored as triglycerides (in fat droplets). Under the influence of **insulin**, adipose cells can also synthesize fatty acids from glucose and amino acids.

(c) Lipid storage is stimulated by **insulin**, which increases the rate of synthesis of lipoprotein lipase and the uptake of glucose and amino acids by adipose cells.

(d) Release of lipids is affected by neural impulses and/or adrenaline. Stored triglycerides are hydrolyzed by **hormone-sensitive lipase**, which is activated by cyclic adenosine monophosphate. The free fatty acids are released into the ECM and then enter the capillary lumen.

CLINICAL CONSIDERATIONS

Recent investigations studying the cellular components of white adipose tissue disclosed that it has a 100-fold richer supply of stem cells, referred to as **adipose-derived stem cells**, than does bone marrow. These cells have the amazing capacity of being able to be reengineered to form chondrocytes, myoblast, and osteoblasts as well as adipocytes. In fact, some surgeons are using the patient's own adipose-derived stem cells that can be isolated within an hour after procuring fat from the patient to remodel and "plump-up" tissues at amputation sites to make it more comfortable for patients sitting in wheel chairs. Additionally, other investigators utilizing goats and rabbits afflicted with osteoarthritis are employing 3D printing technology to engineer cartilage using the animals' own adipose-derived fat cells to seed an artificial matrix, which, after certain manipulations, are implanted into the animal's joints to replace damaged cartilage. Treated animals regained normal motility and showed no evidence of pain. Studies are underway to use the same technology to treat humans suffering from osteoarthritis and other joint problems.

(2) **White adipose tissue** is also an **endocrine organ** that produces a number of hormones known as **adipokines** (Table 4.3). Some of these hormones, **leptin**, **adiponectin**, **resistin**, and **retinol-binding protein-4** are manufactured by adipocytes, whereas other hormones/factors (namely, **tumor necrosis factor-α** [**TNF-α**], **interleukin-6** [**IL-6**], and **adipocyte fatty acid–binding protein**) are produced by the macrophages that reside in adipose tissue of obese individuals. Research suggests that obesity is always accompanied by **chronic inflammation**, and inflammatory agents released in response to inflammation-damaged tissue elicit a recruitment of macrophages into the connective tissue stroma among the enlarged adipocytes.

(a) **Leptin** is a protein hormone, produced primarily by adipocytes, which inhibits appetite for extended periods of time by binding to the appetite increasing neuropeptide Y, thus suppressing the area of the hypothalamus that controls feeding and induces the regions of the hypothalamus that controls the disbursement of energy. Additionally, leptin also induces the synthesis and release of the appetite-repressing neuropeptide α-melanocyte–stimulating hormone. Individuals who have mutations in the leptin gene or in the receptors for leptin exhibit uncontrollable hunger and become obese as a result. In obese people, the volume of each adipocyte and the number of adipocytes is greater than in thin individuals; therefore; the blood leptin levels of obese individuals may be as much as seven times greater than in thin individuals.

(b) **Adiponectin** is also a protein hormone produced only by unilocular adipocytes. This hormone increases insulin sensitivity and therefore facilitates the uptake of glucose and the oxidation of fatty acids in skeletal muscle cells and decreases gluconeogenesis and glucose release by hepatocytes. Thus, adiponectin regulates the body's energy metabolism and facilitates weight loss. The blood levels of this hormone are greater in thin than in obese individuals.

(c) **Resistin** is a peptide hormone that is manufactured by adipocytes in rodents but by macrophages in humans. This hormone may induce **insulin resistance**, resulting in hyperglycemia and type 2 diabetes mellitus in obese patients. Additionally, resistin

table 4.3 Adipokine Origin and Function

Adipokine	Cells of Origin	Function
Leptin	Adipose cells	Reduces appetite by binding to neuropeptide Y
Adiponectin	Adipose cells	Reduces glucose release by liver; increases insulin sensitivity of skeletal muscle cells; facilitates weight loss
Resistin	Macrophages* in humans	Induces insulin resistance; contributes to inflammatory response; promotes glucose release by liver
Retinol-binding protein-4	Adipose cells	Induces insulin resistance; contributes to inflammatory response; promotes glucose release by liver
Tumor necrosis factor-α	Macrophages*	Principal cause of insulin resistance; impedes cells of the liver from oxidizing fatty acids
Interleukin-6	Macrophages*	Increases insulin resistance; promotes glucose uptake by skeletal muscle cells
Adipocyte fatty acid–binding protein	Macrophages*	Denotes the presence of metabolic syndrome and has adverse effects on the cardiovascular system
Apelin	Adipose cells	May reduce pulmonary arterial hypertension and induce nitrous oxide–dependent vasodilation
Vaspin	Adipose cells	Increases insulin sensitivity in mice but its effect in humans is not clear

*Macrophages resident in adipose tissue.

contributes to the inflammatory response, a common finding in insulin resistance, obesity, and type 2 diabetes mellitus.

(d) **Retinol-binding protein-4** is also produced by unilocular adipocytes and it has been demonstrated to elevate insulin resistance, inflammation, and fatty liver disease with a concomitant increase in glucose output by hepatocytes.

(e) **TNF-α** is manufactured by macrophages that reside in adipose tissues of obese individuals and is believed to be the principal cause of insulin resistance. Additionally, TNF-α depresses liver cells' ability to oxidize fatty acids.

(f) **IL-6** is also manufactured and released by macrophages in the connective tissue interstices of unilocular adipose tissue of obese individuals. Similar to TNF-α, IL-6 increases insulin resistance but also enhances skeletal muscle cells' ability to take up glucose and oxidize fatty acids.

(g) **Adipocyte fatty acid–binding protein**, manufactured by macrophages residing in the fibrous connective tissue compartment of adipose tissue, is present in obese individuals in much greater concentration than in slim persons. Its presence is indicative of possible cardiovascular issues, although it may not be a causative factor.

(h) **Apelin**, a peptide, is manufactured by adipocytes as well as by several other cell types, such as hepatocytes, neurons, and cardiac muscle cells. Its synthesis by fat cells is promoted by insulin, and it is present in elevated levels in obese individuals. It may reduce pulmonary arterial hypertension and appears to mitigate the effects of angiotensin II by inducing nitrous oxide–dependent vasodilation.

(i) **Vaspin**, a serine protease inhibitor, is manufactured by visceral adipose cells. It has been demonstrated to increase insulin sensitivity in mice, but its effect in humans is not clear.

CLINICAL CONSIDERATIONS

Recently, obesity has been reclassified as a disease. Individuals are said to be obese if their adipose tissue buildup results in a body mass index greater than 30 kg/m^2 with an increase in the possibility of acquiring a group of health problems referred to as **metabolic syndrome** and a resultant decrease in lifespan. Insulin resistance, type 2 diabetes mellitus, fatty liver disease, and cardiovascular disease are commonly included under the rubric of metabolic syndrome.

Obesity occurs as either **hypertrophic obesity**, characterized by an increase in adipose cell **size** resulting from increased fat storage (**adult onset**), or **hypercellular** (**hyperplastic**) **obesity**, characterized by an increase in the **number** of adipose cells that begins in childhood and is usually lifelong.

A genetic basis for obesity is the result of mutations in the gene for the hormone leptin or in the genes for leptin receptors, thus preventing the production of leptin or producing an inactive form of the hormone or producing inactive leptin receptors. Because leptin functions in the regulation of appetite, persons affected by either of these two conditions possess an insatiable appetite bringing about unrestrained weight gain.

Prader–Willi syndrome is another type of genetic-based obesity that affects 1 in 20,000 to 30,000 individuals, males and females equally. In most cases, the condition is due either to a deletion of genes in the father's chromosome 15 or to the duplication of genes in the mother's chromosome 15 (with the absence of the alleles on the father's side). Symptoms present in infancy include almond-shaped eyes; hypotonia, which is evidenced by the baby feeling like a "rag doll" when held as well as by reduction in the suckling reflex; difficulty in arousing the baby from sleep; and poorly developed, small genitals. The young child exhibits demand for food and rapid weight gain, hypogonadism, short stature, poor muscular coordination, cognitive disability and low IQ (although, in some patients, the IQ is at the lower end of normal), and sleep apnea. Patients afflicted with this syndrome are constantly hungry; they become morbidly obese. They suffer from early type 2 diabetes; hypertension; high LDL levels; and, frequently, cardiovascular problems. These individuals are sterile and present with intellectual and learning disabilities.

b. Brown adipose tissue is composed of **multilocular** adipose cells, which contain many large mitochondria. They are located mostly along the vertebral column, above the kidneys, and in the supraclavicular region.

(1) This tissue is capable of **generating heat** by **uncoupling oxidative phosphorylation**. **Thermogenin**, a transmembrane protein in mitochondria, causes the release of protons away from adenosine triphosphate synthesis, resulting in heat production.

(2) This tissue is found in infants (also in hibernating animals) and is much reduced in adults.

c. Beige adipose cells (brownlike; brite adipose cells) are multilocular fat cells with one large and numerous small fat globules in their cytoplasm. They are intermingled with white adipocytes, especially in the inguinal region. They appear to have an intermediary function between white and brown fat cells.

CLINICAL CONSIDERATIONS

Adipose tumors may be either benign or malignant. **Lipomas** are benign fatty tissue tumors usually found in subcutaneous connective tissues of the neck, back, and proximal regions of the limbs of middle-aged and elderly persons.

Liposarcomas are the most common malignant adipose tumors. Although liposarcomas are most frequently located in the leg and/or the retroperitoneal tissues, they are not restricted to these sites. Liposarcomas are difficult to diagnose as they resemble lipomas. Adipocytes of the malignant tissue resemble either unilocular or multilocular adipocytes. Presently, chromosome markers are used to differentially diagnose liposarcomas.

CLINICAL CONSIDERATIONS

During physical exercise, skeletal muscle cells release the hormone **irisin** that enhances the maintenance of neuromuscular synapses. Irisin may also convert certain unilocular adipocytes into multilocular adipocytes, but that function has been called into question.

C. Specialized connective tissue

1. Blood is discussed in Chapter 5.

2. Cartilage and bone are discussed in Chapter 6.

Review Test

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

Questions 1 through 4 refer to the following scenario:

A patient moved to Virginia from Maine in late winter, and now, in the early spring, he sees his physician concerning symptoms ranging from runny nose, teary eyes, and a productive cough. Because the patient has no fever or muscle aches, the doctor should consider a probable allergic reaction.

1. Which cells are responsible for most of the symptoms?

(A) Neutrophils
(B) Eosinophils
(C) Mast cells
(D) Plasma cells
(E) Pericytes

2. What does the cell that is responsible for the symptoms release to control the reaction it initiated?

(A) Heparin
(B) Leukotriene C_1
(C) Thromboxane A_2
(D) Aryl sulfate
(E) Histamine

3. What triggers the cell that is responsible for most of the patient's symptoms to perform its function?

(A) Arachidonic acid
(B) Plasma cells
(C) Neutrophils
(D) Aryl sulfatase
(E) IgE cross-linking

4. Usually the reaction is localized, but it may become systemic and then the patient will experience

(A) burning eyes.
(B) uncontrolled sneezing.
(C) hyperventilation.
(D) bradycardia.
(E) anaphylactic shock.

Questions 5 through 8 refer to the following scenario:

A 3-year-old child is brought to the pediatrician by his parents because he has gained a lot of weight in the past few months and is constantly hungry. The pediatrician notes that the child has short stature, underdeveloped penis and testes, and hypotonia.

5. What chromosomal anomaly should the pediatrician suspect based on her examination of the child?

(A) Trisomy 21
(B) Monosomy 15
(C) XXY
(D) Missing X chromosome
(E) Missing Y chromosome

6. This child is susceptible to a number of health problems, including

(A) hyperthyroidism.
(B) hypothyroidism.
(C) hypotension.
(D) hypertension.
(E) type 1 diabetes.

7. A patient had a complete blood count performed, and the results showed an increased eosinophil level but all other counts were normal. The internist should suspect that the patient is suffering from which of the following?

(A) Acute inflammation
(B) Chronic inflammation
(C) Parasitic infection
(D) Tetanus
(E) Lymphoma

8. Synovial fluids of normal joints are usually devoid of collagen. Patients with rheumatoid diseases have various types of collagen in their synovial fluid, depending on the tissue being damaged. If a patient has type II collagen in the

synovial joint, which of the following tissues is being eroded?

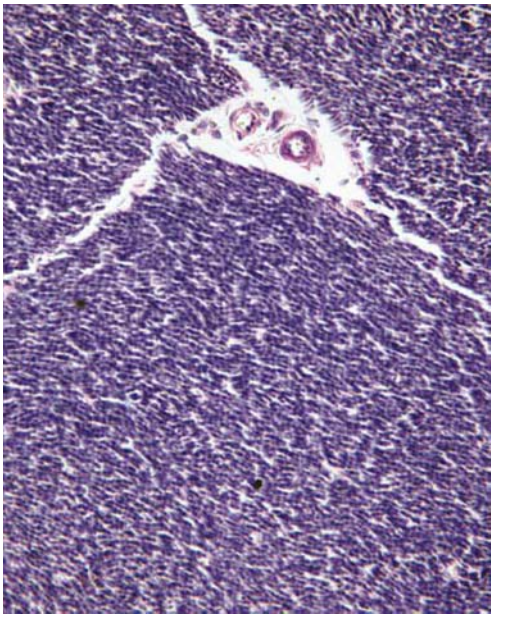
(A) Vascular endothelium
(B) Compact bone
(C) Vascular smooth muscle
(D) Articular cartilage
(E) Synovial membrane

9. Which one of the following statements concerning loose connective tissue is true?

(A) It is less abundant than dense connective tissue.
(B) It has a lower proportion of cells to fibers than does dense connective tissue.
(C) It acts as a medium for exchange of nutrients and wastes between the blood and tissues.
(D) It provides structural support for organs.
(E) It consists of many fibers in which various types of cells are embedded.

10. Question 10 refers to the figure below:

This photomicrograph is a normal area of a cancerous tumor from a young child. Where was the cancer located?



(A) Tendon
(B) Aponeurosis
(C) Ligament
(D) Capsule of the kidney
(E) Along the spinal column

Answers and Explanations

1. **C.** Mast cells release a number of pharmacologic agents, including histamine, which is responsible for most of the symptoms that the patient presents.
2. **A.** Heparin is an anticoagulant and also responsible for inactivating histamine.
3. **E.** Cross-linking of IgE occurs when antigens bind to the immunoglobulins. This reaction causes the mast cells to degranulate and also to activate enzymes that convert arachidonic acid to various secondary mediators.
4. **E.** Anaphylactic shock occurs when mast cell degranulation is systemic and the body is overwhelmed with the released pharmacologic agents. In extreme cases, the individual may undergo respiratory and cardiovascular shock, and, if untreated shortly after the onset of the reaction, the person may die.
5. **B.** The child is probably suffering from Prader–Willi syndrome, in which the paternal chromosome 15 was deleted during the father's meiosis.
6. **D.** Older patients with Prader–Willi syndrome suffer from hypertension; type 2 diabetes; high LDL levels; sterility; cardiovascular problems; and, frequently, low IQ.
7. **C.** During parasitic infections, a patient's eosinophil levels become increased because these leukocytes destroy parasites.
8. **D.** Type II collagen is present only in hyaline and elastic cartilages; therefore, finding type II collagen in the synovial fluid of a joint indicates erosion of the articular cartilage.
9. **C.** Both loose and dense connective tissues are composed of three elements: an amorphous ground substance, fibers, and various types of cells. The amorphous ground substance of loose connective tissue is the medium of exchange between the connective tissue cells and the bloodstream.
10. **E.** Because the photomicrograph presents dense regular elastic fibers, the tumor had to be along the spinal column. The tendon, aponeurosis, and ligament are composed of dense regular collagenous connective tissue, and the capsule of the kidney is a dense irregular collagenous connective tissue.

chapter 5

Blood and Hemopoiesis

I. OVERVIEW—BLOOD

A. Blood, **a specialized connective tissue that consists of formed elements (*erythrocytes, leukocytes, and platelets*) and a fluid component called *plasma*, circulates in a closed system of vessels and *transports* nutrients, waste products, hormones, proteins, ions, oxygen (O_2), carbon dioxide (CO_2), and formed elements.** It also **regulates body temperature** and assists in regulation of **osmotic** and **acid–base balance.**

B. **The volume of blood in an average human adult is approximately *5 L*.** Blood cells have short life spans and are continuously replaced by a process called hemopoiesis.

II. BLOOD CONSTITUENTS

A. Plasma **consists of 90% *water*, 9% *organic compounds* (such as proteins, amino acids, and hormones); and 1% *inorganic salts*, dissolved *gases*, and *nutrients*.**

1. **Main plasma proteins**
   a. **Albumin**, a small protein (66.5 kDa), preserves the colloid osmotic pressure in the vascular system and helps transport some metabolites. Colloid osmotic pressure assists in maintaining proper blood volume by resisting the exit of plasma from the blood stream. Recall that **plasma** that leaves blood vessels to enter the connective tissue spaces is known as **extracellular fluid** (**tissue fluid**).
   b. **γ-Globulins** are **antibodies** (**immunoglobulins**).
   c. **α-Globulins** and **β-globulins** transport metal ions (e.g., iron and copper) and lipids (in the form of lipoproteins).
   d. Clotting proteins, including **fibrinogen**, a soluble protein that is converted into fibrin during blood clotting
   e. **Complement proteins** (C1–C9) are part of the **innate immune system**, and function in non-specific host defense, and initiate the inflammatory process.
2. **Serum** is the **yellowish fluid** that remains after blood has clotted. It is similar to plasma but lacks fibrinogen and clotting factors.

B. Formed elements of blood **(Table 5.1 and Fig. 5.1)**

1. **Erythrocytes** (**red blood cells**; **RBCs**)
   a. **General features**
      (1) RBCs are round, biconcave cells that **stain light salmon pink** with either Wright or Giemsa stains (see Fig. 5.1). Several **cytoskeletal proteins** (ankyrin, band 4.1 and band 3 proteins, spectrin, and actin) maintain the biconcave shape of these cells. Mature erythrocytes possess no nuclei or organelles but are filled with **hemoglobin** (**Hb**). Erythrocytes also

table 5.1 Size and Number of Formed Elements in Human Blood

Cell Type	Diameter (μm)		Cells/mm³ of Blood	Leukocytes (%)
	Smear	Section		
Erythrocyte	7–8	6–7	5×10^6 (men)	–
			4.5×10^6 (women)	
Agranulocytes				
Lymphocyte	8–10	7–8	1,500–2,500	20–25
Monocyte	12–15	10–12	200–800	3–8
Granulocytes				
Neutrophil	9–12	8–9	3.500–7.000	60–70
Eosinophil	10–14	9–11	150–400	2–4
Basophil	8–10	7–8	50–100	0.5–1
Platelet	2–4	1–3	250,000–400,000	–

Reprinted from Gartner LP, Hiatt, JL. *Color Atlas of Histology*. 2nd ed. Baltimore, MD: William & Wilkins; 1994:94.

contain **soluble enzymes** that are responsible for glycolysis, the hexose monophosphate pathway, and the production of adenosine triphosphate (ATP).

(2) The average life span of erythrocytes is 120 days. Old cells are fragile and express specific oligosaccharides on their surface that are recognized by splenic, hepatic, and bone marrow macrophages, which destroy those erythrocytes.

(3) **A**, **B**, and **O antigens**, located on the external surface of the erythrocyte's plasmalemma, are short sequences of carbohydrate molecules that are almost identical to each other. All three are attached to the extracellular moiety of transmembrane proteins (**glycophorins**). Types A and B antigens have an additional terminal sugar molecule attached

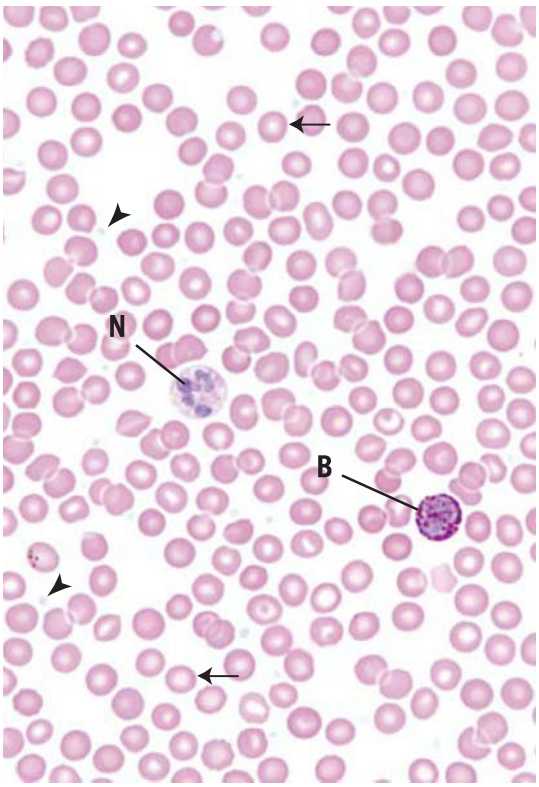


FIGURE 5.1. Light micrograph of a human blood smear. Wright stain (×540). B, basophil; N, neutrophil; *arrows*, erythrocytes; *arrowheads*, platelets.

to the carbohydrate chain of type O antigens. The addition of the terminal carbohydrate molecule requires enzymes (***N*-acetylgalactosamine transferase** in type A and **galactose transferase** in type B) whose presence is genetically determined.

(a) In type AB, both enzymes are present; therefore, RBCs possess both A and B antigens on their cell membranes.

(b) In type O, neither enzyme is present; therefore, only type O antigens are located on the RBC cell membrane.

CLINICAL CONSIDERATIONS

Blood type AB is the **universal acceptor**; therefore, an individual with AB blood type can receive a transfusion from individuals whose blood type is A, B, AB, or O. Blood type O is the **universal donor**, so that an individual with blood type O can give blood to individuals whose blood type is A, B, AB, or O.

(4) **Rh blood type antigens** are of various types, but the most important one is the **D antigen** (**Rh factor**) because it is prone to result in the greatest immunogenic response and is responsible for **erythroblastosis fetalis** in the newborn. ("Rh" is for **Rhesus monkey** whose blood cells were used in the original work on this antigen.) A particular individual's erythrocytes either express (Rh positive, **Rh^+**) or do not express (Rh negative, **Rh^-**) the D antigen.

CLINICAL CONSIDERATIONS

When an Rh^- mother carries an Rh^+ fetus, the fetus's erythrocytes may come in contact with the mother's blood during the third trimester or during the birth process. The Rh^- mother's immune system will produce IgM antibodies against the D antigen, but these antibodies are too large to go through the placental barrier. During a subsequent pregnancy with another Rh^+ fetus, the mother will again produce antibodies, but this time they will be IgG antibodies. These are small enough to penetrate the placental barrier and mount an immune response against the fetus. This condition is known as **erythroblastosis fetalis** and may be lethal to the fetus. In order to protect future fetuses, the Rh^- mother who has an Rh^+ child is given anti-D globulin (**RhoGAM**) after the baby is born. The anti-D globulin attaches to the antigenic sites of the D antigen so that the mother's immune system does not recognize it and does not produce antibodies against the D antigens, thus protecting future Rh^+ fetuses from the mother's immune system.

b. **Hematocrit** is expressed as a percent estimate of the **volume of packed erythrocytes per unit volume of blood**.

(1) Normal values for adults are 40% to 50% in men and 35% to 45% in women.

(2) Normal values in children are 45% to 60% in newborns and 35% in those up to age 10 years.

c. **Hb** is a protein composed of four polypeptide chains, each covalently linked to a heme group. The four chains that normally occur in humans are α, β, γ, and δ, whose amino acid sequences differ from each other. Hb occurs in several normal forms with different chain compositions.

(1) The predominant form of adult Hb is **HbA_1** ($\alpha_2\beta_2$).

(2) A minor form is **HbA_2** ($\alpha_2\delta_2$).

(3) Fetal Hb is designated **HbF** ($\alpha_2\gamma_2$).

d. **Transport of** CO_2 and O_2 to and from the tissues of the body is carried out by erythrocytes and plasma.

(1) About 200 mL of CO_2 is formed every minute by cells of the body making the partial pressure of CO_2 higher in the tissue than in the capillaries; thus, CO_2 enters the capillaries via simple diffusion.

(a) Twenty milliliters of the CO_2 is transported in the plasma, 40 mL binds to the globin moiety of Hb (forming **carbaminohemoglobin**), and 140 mL enters the RBC cytosol.

(b) The enzyme **carbonic anhydrase** of the RBC cytosol forms H_2CO_3 by combining CO_2 with H_2O. H_2CO_3 dissociates; HCO_3^- leaves the RBC to enter the plasma and Cl^- from the plasma enters the RBC cytosol to maintain electrical equilibrium. This exchange of ions between the cytosol and the plasma is the **chloride shift**.

(c) Meanwhile, because the partial pressure of O_2 is greater in the RBC than in the tissue, the O_2 is released from the Hb, forming **deoxyhemoglobin**, and the place of O_2 is taken up by the binding of **2,3-diphosphoglycerate**.

(2) The partial pressure of O_2 is greater in the lungs' alveolar airspaces than in the capillaries; therefore, O_2 enters the capillaries via simple diffusion.

(a) O_2 enters the erythrocyte cytosol and binds to the heme moiety of the Hb molecule to form **oxyhemoglobin**.

(b) Bicarbonate ions of the plasma reenter the RBC cytosol, and, in exchange, Cl^- ions leave the RBC to enter the plasma (a reversal of the chloride shift). The bicarbonate ion is combined with H^+ ions to form H_2CO_3, which is cleaved by carbonic anhydrase to form CO_2 and H_2O. The CO_2 enters the plasma, and, from there, it enters the alveolar airspace via simple diffusion to be exhaled.

(3) Because **carbon monoxide** (**CO**) binds avidly to Hb, it can block binding of O_2 and cause **carbon monoxide asphyxiation** if it is inhaled in sufficient amounts.

(4) **Nitric oxide** (**NO**) is a neurotransmitter substance that binds to Hb; in areas that are O_2-poor, it facilitates dilation of blood vessels and a more efficacious exchange of O_2 for CO_2.

CLINICAL CONSIDERATIONS

Sickle cell anemia is most often caused by a point mutation in the DNA encoding the Hb molecule, leading to production of an **abnormal Hb** (HbS). In the β-chain of HbS, the amino acid **valine** is substituted for **glutamate**. This disease affects 1 in 500 African Americans and 1 in 1,000 to 1,400 people of Hispanic American heritage in the United States. HbS crystallizes under low O_2 tension, giving RBCs the characteristic sickle shape. **Sickle RBCs** are fragile and have a **higher rate of destruction** than normal cells. People with sickle cell anemia exhibit hypoxia, increased bilirubin levels, low RBC count, and capillary stasis.

Pernicious anemia is caused by a severe **deficiency of vitamin B_{12}**, resulting from impaired production of **gastric intrinsic factor** by the parietal cells of the gastric mucosa. This factor is required for the proper absorption of vitamin B_{12}.

Newborns are commonly deficient in **vitamin K**, an essential cofactor for the clotting process, and if they do not receive exogenous administration of this vitamin, they may die from **hemorrhagic disease of the newborn**. Adults who are unable to absorb lipids may also suffer from excessive bleeding, but the supplemental injection of vitamin K improves this condition.

Malaria is a mosquito (*Anopheles* sp.)-borne disease caused by five species of the parasite genus *Plasmodium*. The most serious form of malaria that causes most deaths is due to infection with *Plasmodium falciparum*. An individual stricken with malaria experiences vomiting, headaches, malaise, and fever that can, if untreated, lead to seizures and coma and in many cases, death. It was always suspected that mosquitoes were especially attracted to people infected with malaria but the reason was not understood. Recent studies noted that the *Plasmodium* releases (***E*)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate** (**HMBPP**) into the infected person's blood, and HMBPP causes the infected RBCs to release more CO_2 than do normal erythrocytes, a mosquito attractant. Additionally, infected RBCs also release monoterpenes and aldehydes, which also attract mosquitoes.

Leukocytes (**white blood cells**; **WBCs**) (Table 5.1 and Fig. 5.1)

a. General features: The two main categories of **leukocytes** are **granulocytes** and **agranulocytes**, depending on the presence (in granulocytes) or absence (in agranulocytes) of **specific granules** in their cytoplasm (**azurophilic granules** are present in both WBC categories and are, in fact, **lysosomes**).

b. Granulocytes (Table 5.2) are of three types: **neutrophils**, **eosinophils**, and **basophils** (Fig. 5.2; also see Fig. 5.1).

(1) Granulocytes possess **specific granules** with type-specific contents; they generate ATP via the Krebs cycle (eosinophils and basophils) and anaerobic pathways (neutrophils).

(2) Destruction of phagocytosed microorganisms by neutrophils occurs in two ways.

(a) Azurophilic granules release **hydrolytic enzymes** into phagosomes to destroy microorganisms.

(b) Reactive O_2 compounds, **superoxide** (**O_2^-**), hydrogen peroxide (H_2O_2), and hypochlorous acid (HOCl), formed within phagosomes (catalyzed by **myeloperoxidase**), a process known as **respiratory burst**, destroy microorganisms.

table 5.2 Selected Characteristics of Granulocytes

Characteristic	Neutrophils	Eosinophils	Basophils
Nuclear shape	Lobulated (3 or 4 lobes)	Bilobed	S-shaped
Number of azurophilic granules	Many	Few	Few
Specific granules			
Size	Small	Large	Large
Color*	Light pink	Dark pink	Dark blue to black
Contents	Alkaline phosphatase Collagenase	Acid phosphatase Arylsulfatase	Eosinophil chemotactic factor
	Lactoferrin	β-Glucuronidase	Heparin
	Lysozyme	Cathepsin	Histamine
	Phagocytin	Major basic protein	Peroxidase
		Peroxidase	
		Phospholipase	
		Ribonuclease	
Life span	1 week	Few hours in blood, 2 weeks in connective tissue	Very long (1–2 years in mice)
Main functions	Phagocytose, kill, and digest bacteria	Moderate inflammatory reactions by inactivating histamine and leukotriene C	Mediate inflammatory responses in a manner similar to mast cells
Special properties	Form H_2O_2 during phagocytosis	Are decreased in number by corticosteroids	Have receptors for immunoglobulin E on their plasma membrane

*Cells stained with Giemsa or Wright stains.

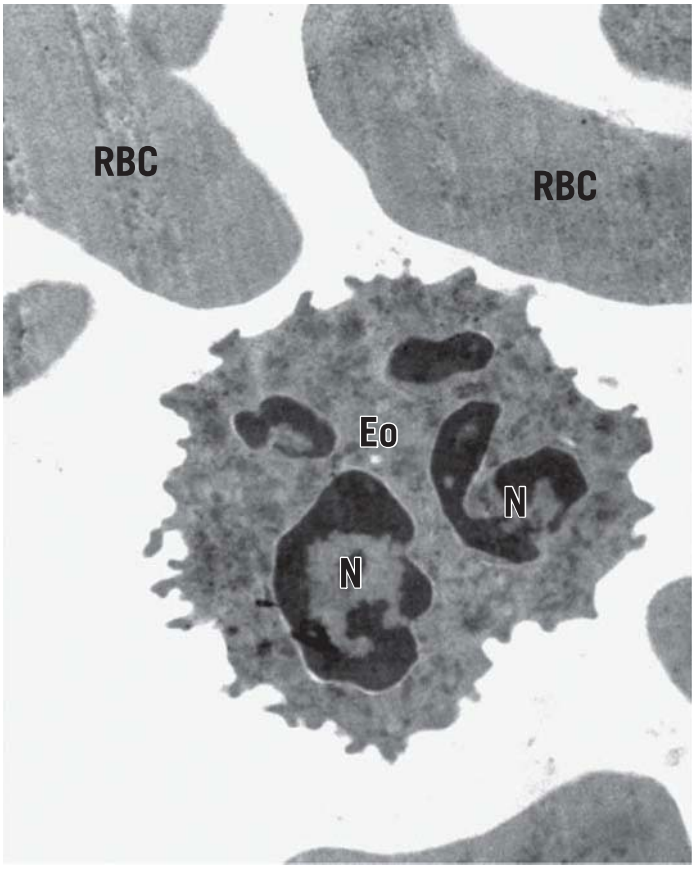


FIGURE 5.2. This electron micrograph of an eosinophil (Eo) displays the bilobed nucleus (N) and the granular appearance of the cytoplasm. Several erythrocytes (RBC) are also evident. (Courtesy of Dr. Zulmarie Franco.)

table 5.3 Selected Characteristics of Agranulocytes

Characteristic	Monocytes	T Lymphocytes	B Lymphocytes
Plasma membrane	Form filopodia and pinocytic vesicles	Have T-cell receptors	Have Fc receptors and antibodies
Number of azurophilic granules	Many	Few	Few
Life span	Less than 3 days in blood	Several years	Few months
Main functions	Become macrophages in connective tissue	Generate cell-mediated immune response, secrete numerous growth factors	Generate humoral immune response

c. **Agranulocytes** (Table 5.3 and Fig. 5.3), namely **lymphocytes** and **monocytes**, lack specific granules. (See Chapter 10 for a more complete discussion of lymphocytes and monocytes.)
   (1) The three categories of lymphocytes are **B lymphocytes**, **T lymphocytes**, and **null cells**. Generally speaking, B lymphocytes are responsible for the humoral immune response, and T lymphocytes are responsible for the cellular immune response. Null cells constitute approximately 5% of the circulating lymphocytes and are of two types, pluripotential hemopoietic stem cells (PHSCs) and natural killer (NK) cells. Null cells resemble lymphocytes but lack their characteristic surface determinants.

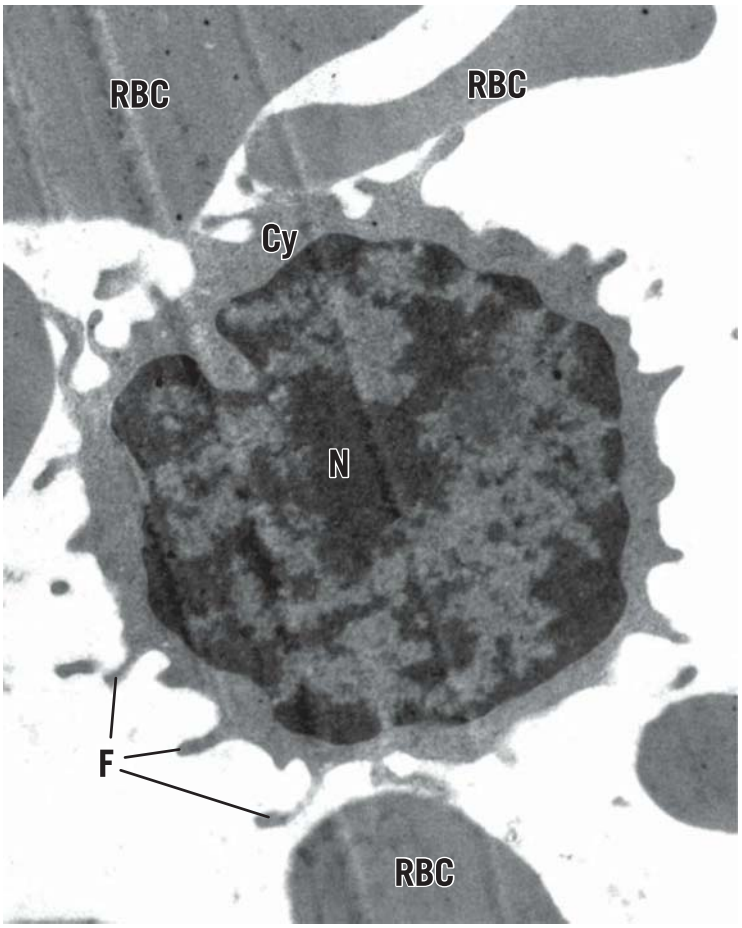


FIGURE 5.3. This electron micrograph of a lymphocyte displays the large nucleus (N) surrounded by a thin rim of cytoplasm (Cy). Several erythrocytes (RBC) are also evident. F, filopodia. (Courtesy of Dr. Zulmarie Franco.)

CLINICAL CONSIDERATIONS

Infectious mononucleosis is caused by the **Epstein–Barr virus** (**EBV**), a relative of the herpes virus. This disease mostly affects young individuals of high school and college age and the virus may be transmitted by saliva (as in kissing) with an incubation period of 1 to 2 months. Signs and symptoms of infectious mononucleosis include fatigue, swollen and tender lymph nodes, splenomegaly, fever, sore throat, and an increase in circulating lymphocytes. Although usually benign, the condition may be life-threatening in immunosuppressed or immunodeficient individuals. Other conditions such as cytomegalovirus infection, pharyngitis, toxoplasmosis, influenza, HIV infection, leukemia, and tonsillitis can all mimic mononucleosis and should be ruled out by the examining physician.

Burkitt lymphoma is a noninherited, aggressive tumor of the **B lymphocytes**, a non-Hodgkin lymphoma. The three forms are **endemic** (**African variant**), **sporadic** (**non-African**), and **immunodeficiency-associated**. Not only do all three forms have a similar appearance when viewed with the microscope, but also all three forms appear to be caused by mutations in a regulator gene that codes for a nuclear phosphoprotein that acts as a transcription factor in the progression of the cell cycle (**c-Myc gene**) in conjunction with translocations of genes that code for immunoglobulins.

The **endemic** form is most common in regions of the world where malaria is endemic and occurs in common with infection by the EBV. The condition first appears as tumors in the orofacial region from where it spreads to the breasts, ovaries, gastrointestinal tract, and the brain.

The **sporadic form** is common in regions of the world where malaria is not endemic; only 20% is associated with EBV. The condition first appears in the intestines forming large abdominal tumors that may invade the spleen, bone marrow, liver, and the brain. The **immunodeficiency-associated form** is present in individuals infected with the HIV (40% of cases are associated with EBV). Similar to the sporadic form, the condition first appears in the intestines forming large abdominal tumors that may invade the spleen, bone marrow, liver, and the brain. It is fatal if untreated, but aggressive chemotherapy can offer a cure in 70% of cases if caught early and 50% of cases if it has not involved the bone marrow or the central nervous system (CNS), but only 20% of cases if the CNS and bone marrow are involved.

Leukemias are characterized by the replacement of normal hemopoietic cells of the bone marrow by neoplastic cells and are classified according to the **type** and **maturity** of the cells involved.

Acute leukemias occur mostly in children and involve **immature cells. Rapid onset** of the following signs and symptoms occur: anemia; high WBC count and/or many circulating immature WBCs; low platelet count; tenderness in bones; enlarged lymph nodes, spleen, and liver; vomiting; and headache.

Chronic leukemias occur mainly in adults and initially involve relatively **mature cells**. Early signs include **slow onset** of a mild leukocytosis and enlarged lymph nodes; later signs and symptoms include anemia, weakness, enlarged spleen and liver, and reduced platelet count.

3. **Platelets** (**thrombocytes**) (Table 5.4; also see Table 5.1 and Fig. 5.1) are anucleate disk-shaped cell fragments that arise from megakaryocytes in bone marrow. Platelets are surrounded by a **glycocalyx**, which coats the plasmalemma and is composed of the extracellular components of integral proteins (**glycoprotein Ib** [**GPIb**]), glycosaminoglycans, GPs, and various coagulation factors. **Calcium ions** and **adenosine diphosphate** (ADP) increase the stickiness of the glycocalyx and enhance platelet adherence.
   - **a.** A clear peripheral region, the **hyalomere**, and a region containing purple-colored granules, the **granulomere**, are visible in stained blood smears.
     - **(1)** The **hyalomere**, as viewed with the electron microscope, is occupied by a small bundle of 10 to 12 circularly disposed **microtubules** that mirror and assist in maintaining the discoid shape. Additional cytoskeletal elements, such as **actin**, **myosin**, and various proteins that bind the cytoskeletal components to each other and the plasmalemma, are present. The two systems of cytoplasmic channels are the **open canalicular system** that communicates with the extracellular space and the **dense tubular system** that does not communicate with the extracellular space.

table 5.4 Platelet Components

Hyalomere		Granulomere			
Structure	Function	Granules	Size (nm)	Contents	Function
Actin and myosin	Platelet contraction	α	300–500	Fibrinogen, platelet thromboplastin, factors V and VIII, platelet-derived growth factor	Repair of vessel, platelet aggregation, coagulation
Microtubule bundles	Maintains platelet shape	δ (dense bodies)	250–300	Pyrophosphate, adenosine diphosphate, adenosine triphosphate, histamine, serotonin, Ca^{2+}	Vasoconstriction, platelet aggregation and adhesion
Surface opening tubule system	Facilitates exocytosis and endocytosis in activated platelets	λ	200–250	Lysosomal enzymes	Clot removal
Dense tubular system	Prevents platelet stickiness by sequestering Ca^{2+}				

(2) The **granulomere** is occupied by three types of granules, alpha, delta, and gamma granules, where the last named are **lysosomes** (Table 5.4 describes the contents and functions of these thromboplastic elements).

b. Platelets function in **blood coagulation** by aggregating at lesions in vessel walls and producing various factors that aid in clot formation.

(1) Blood coagulation contributes to hemostasis (stoppage of bleeding) and is normally controlled very stringently so that it occurs **only in regions where the endothelium is damaged**.

(2) Blood coagulation occurs via two interrelated pathways, the **extrinsic** and **intrinsic pathways**, where both involve platelets**.** The final steps in both pathways, referred to as the **common pathway**, involve the transformation of **prothrombin** to **thrombin**, an enzyme that catalyzes the conversion of **fibrinogen** (**factor I**) to **fibrin monomers**, which, under the influence of **Ca^{2+} ions** and **factor XIIIa**, coalesce to form a **reticulum of clot**.

(3) Once the blood vessel is repaired, the clot is no longer necessary and has to be removed. This process is initiated by **tissue plasminogen activator** (**tPA**) and by **urokinase-type plasminogen activator** (**u-PA**) enzymes localized on the luminal cell membranes of endothelial cells and in blood plasma. Both enzymes activate **plasminogen**, an enzyme precursor synthesized by liver cells and released into the blood stream, by converting it to the active enzyme **plasmin**. Together with macrophages, plasmin dissolves the secondary hemostatic plug.

CLINICAL CONSIDERATIONS

Coagulation disorders commonly result from inherited or acquired defects of coagulation factors.

1. **Hemophilia A** (**factor VIII deficiency**) is an X-linked disorder that affects mostly men, but because men contribute a Y chromosome, they cannot pass the condition to their sons. However, they can contribute a defective X chromosome to their daughters, who then become carriers. About 65% of the cases are due to inheritance and 35% are due to spontaneous mutations.

   Severity varies with the extent of reduction in the level of factor VIII (produced by hepatocytes), but approximately half of hemophilia A patients have a **severe condition** (less than 1% factor VIII serum levels) and exhibit excessive spontaneous bleeding episodes, even into joints and muscles. People with **moderate condition** (1%–5% factor VIII serum levels) can also have spontaneous bleeding episodes, but most have prolonged bleeding subsequent to injury. Individuals with the **mild condition** (6%–50% factor VIII serum levels) experience prolonged bleeding after surgery, tooth extraction, or major laceration.

Affected individuals have a normal platelet count, normal bleeding time, and no petechiae, but **partial thromboplastin time** (**PTT**) is increased. PTT is a measure of the rapidity of clotting because of factors in the intrinsic and common, but ***not*** extrinsic, coagulation pathways. Routine treatment is usually not necessary in mild or moderate conditions, but factor VIII infusion is necessary prior to surgery or tooth extraction. Severe conditions may require prophylactic factor VIII infusions on a regular basis.

2. **von Willebrand disease** is an autosomal dominant genetic defect, resulting in a **decrease** in the amount of **von Willebrand factor**, which is required in the intrinsic pathway of coagulation. Most cases are mild and do not involve bleeding into the joints. Severe cases are characterized by excessive and/or spontaneous bleeding from mucous membranes and wounds.
3. **Bernard–Soulier syndrome** is an uncommon, autosomal disease that is distinguished by very large platelets (as large as 7 μm in diameter) that do not possess enough GPIb integrin molecules in their plasma membrane. Because of this defect, the platelets cannot form bonds with von Willebrand factor and, therefore, cannot form a primary hemostatic plug resulting in exceptionally severe bleeding.
4. **Glanzmann thrombasthenia** is also an uncommon bleeding disorder, an autosomal recessive trait, in which the platelets of affected individuals possess defective **glycoprotein IIb/IIIa** (**GPIIb/IIIa**). Because this platelet plasmalemma integrin molecule is responsible for binding to fibrinogen and thereby ensuring that platelets of a primary hemostatic plug adhere to each other, a defect in the integrin molecule prevents the formation of a **primary hemostatic plug.** With hemostasis not controlled properly, severe bleeding may occur, with consequent death of the affected individual.
5. **Thrombocytosis** is an elevated platelet count. Although many reasons could account for an increased platelet level, one study showed that prolonged thrombocytosis (for 6 months or more) may be a sign that the individual may develop cancer in the next 12 months (males have an 18% possibility and females, 10%). The most common types of cancer in these individuals were colorectal and lung cancers.

III. BONE MARROW

Bone marrow is a gelatinous substance, is responsible for the formation of the formed elements of blood, is present in the marrow spaces of bone, and exists in two forms: yellow marrow and red marrow.

A. Yellow marrow **is located in the long bones of adults and is highly infiltrated with fat.** It is **not** hemopoietic, but it has the **potential** to become so if necessary.

B. In adults, ***red marrow*** **is located in the epiphyses of long bones and in flat, irregular, and short bones (Fig. 5.4)**. It is highly vascular and composed of a ***stroma***, irregular ***sinusoids***, and islands of ***hemopoietic cells***. Red marrow is the site of blood cell ***differentiation*** and ***maturation***. The largest cells of bone marrow are the ***megakaryocytes*** (Fig. 5.4), which generate platelets.
   1. **Sinusoids** are large venous vessels with highly attenuated (very thin) endothelial cells with large gaps between them. They are associated on their extravascular surfaces with reticular fibers and **adventitial reticular cells**, which manufacture these fibers.
   2. **Stromal cells** include macrophages, adventitial reticular cells, fibroblasts, and endothelial cells. These cells produce and release various **hemopoietic growth factors** (Table 5.5).
      a. **Macrophages** are located in extravascular areas near sinusoids and extend processes between endothelial cells into sinusoidal lumina. These cells phagocytose cast off cytoplasm and extruded nuclei and also transfer iron to differentiating cells of the RBC lineage.
      b. **Adventitial reticular cells** (see Fig. 5.4) are believed to subdivide the bone marrow cavity into smaller compartments, which are occupied by **islands of hemopoietic cells**. Adventitial reticular cells may accumulate fat (instead of fat cells), thus transforming red marrow into yellow marrow.

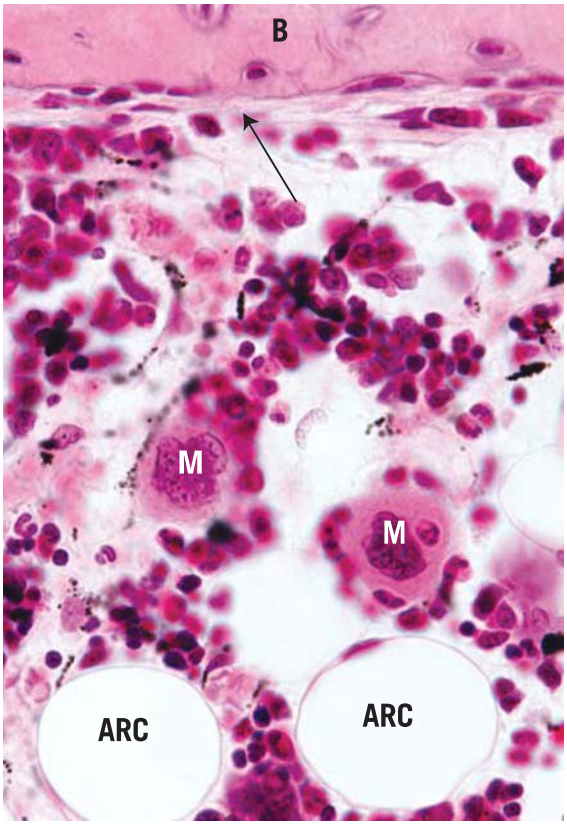


FIGURE 5.4. Light micrograph of a cross section of a human rib displaying its bone marrow. ARC, adventitial reticular cells; B, bone; M, megakaryocytes; *arrow*, endosteum (×540).

IV. HEMOPOIETIC GROWTH FACTORS (COLONY-STIMULATING FACTORS [CSFs])

A. Hemopoiesis **is modulated by a number *growth factors* and *cytokines*, including CSFs, stem cell factor (steel factor), interleukins (ILs), and erythropoietin, thrombopoietin, and a few transcription factors (see Table 5.5). Stem cell factor** is probably the most important of the CSFs because it must be present to maintain a large enough population of pluripotential hemopoietic stem cells (PHSCs) as well as multipotential hemopoietic stem cells and progenitor cells.

B. **These factors may circulate in the bloodstream, acting as hormones, or they may act as local factors produced in the bone marrow that facilitate and stimulate formation of blood cells in their vicinity.**

C. **They act at low concentrations and bind to specific membrane receptors on single target cells.**

D. **Their various effects on target cells include control of mitotic rate, enhancement of cell survival, control of the number of times the cells divide before they differentiate, and promotion of cell differentiation.**

E. Hemopoietic stem cells **that do not contact growth factors, especially stem cell factor, usually enter *apoptosis* and are eliminated by *macrophages*.**

table 5.5 Hemopoietic Growth Factors

Factors	Principal Action of the Factor	Site of Origin of the Factor
Stem cell factor (steel factor, c-kit ligand)	Stimulate proliferation of pluripotential and multipotential stem cells and the formation of mast cells	Stromal cells of bone marrow
GM-CSF	Facilitates CFU-GM mitosis and differentiation; facilitates granulocyte activity	T cells, endothelial cells
G-CSF	Promotes CFU-G mitosis and differentiation; facilitates neutrophil activity	Macrophages, endothelial cells
M-CSF	Facilitates mitosis, differentiation of CFU-M	Macrophages, endothelial cells
IL-1	In conjunction with IL-3 and IL-6, it promotes proliferation of PHSC, CFU-GEMM, and CFU-Ly; suppresses erythroid precursors	Monocytes, macrophages, endothelial cells
IL-2	Promotes proliferation of activated T cells and B cells; facilitates NK cell differentiation	Activated T cells
IL-3	In conjunction with IL-1 and IL-6 it promotes proliferation of PHSC, CFU-GEMM, and CFU-Ly as well as unipotential precursors (except for LyB and LyT); also facilitates proliferation of BFU-E	Activated T and B cells
IL-4	Promotes activation of T cells, B cells; facilitates development of mast cells, basophils; also promotes BFU-E formation	Activated T cells
IL-5	Facilitates proliferation of CFU-Eo; activates eosinophils	T cells
IL-6	In conjunction with IL-1 and IL-3, it promotes proliferation of PHSC, CFU-GEMM, and CFU-Ly; also promotes differentiation of CTLs and B cells	Monocyte, fibroblasts
IL-7	Stimulates CFU-LyB and CFU-LyT; enhances NK cell differentiation	Stromal cells
IL-8	Promotes migration and degranulation of neutrophils	Leukocytes, endothelial cells, smooth muscle cells
IL-9	Promotes activation, proliferation of mast cells, modulates immunoglobulin E synthesis, stimulates proliferation of T helper cells	T helper cells
IL-10	Inhibits synthesis of cytokines by NK cells, macrophages, and T cells; promotes CTL differentiation and B cell and mast cell proliferation	Macrophages, T cells
IL-12	Stimulates NK cells; promotes CTL and NK cell function	Macrophages
IL-15	Promotes NK cell maturation	Macrophages
γ-Interferons	Activates monocytes and B cells; promotes CTL differentiation; enhances expression of class II human leukocyte antigen	T cells, NK cells
Erythropoietin	Promotes CFU-E differentiation, proliferation of BFU-E	Endothelial cells of peritubular capillary network of kidney; hepatocytes
Thrombopoietin	Enhances mitosis and differentiation of CFU-Meg and megakaryoblasts	Hepatocytes and liver sinusoidal lining cells; kidney proximal tubule cells; bone marrow stromal cells
GATA3 transmission factor	Differentiation of T and B lymphocytes	Expressed in relevant cells
Ikaros family of transmission factors	Differentiation of T and B lymphocytes	Expressed in relevant cells
Pax5 transmission factor	B lymphocyte maturation	Expressed in relevant cells
PU.1 transmission factor	Development of granulocytes, macrophages, and B lymphocytes	Expressed in relevant cells

BFU-E, burst-forming unit-erythrocyte; CFU, colony-forming unit; CSF, colony-stimulating factor; CTL, cytotoxic T lymphocyte; Eo, eosinophil; G, granulocyte; GEMM, granulocyte, monocyte, megakaryocyte; GM, granulocyte–monocyte; IL, interleukin; Ly, lymphocyte; M, monocyte; Meg, megakaryocyte; NK, natural killer; PHSC, pluripotential hemopoietic stem cells; S, spleen.
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V. PRENATAL HEMOPOIESIS

This process occurs successively in the yolk sac, liver, spleen, and bone marrow.

A. The bone marrow first participates in hemopoiesis at about 6 months' gestation and assumes an increasingly large role thereafter.

B. The liver and spleen cease hemopoiesis at about the time of birth.

VI. POSTNATAL HEMOPOIESIS

This process involves three classes of cells: **stem**, **progenitor**, and **precursor cells**.

A. Comparison

1. **Stem cells** are capable of **self-renewal** and can undergo enormous proliferation.
   a. These cells can differentiate into **multiple** cell lineages.
   b. They are present in circulation (as null cells) and in bone marrow.
2. **Progenitor cells** have reduced potentiality and are committed to a single-cell lineage.
   a. They **proliferate** and **differentiate** into precursor cells in the presence of appropriate growth factors.
   b. They are morphologically indistinguishable from stem cells and, morphologically, all appear similar to small lymphocytes.
3. **Precursor cells** are all the cells in each lineage that display **distinct morphologic characteristics**. They cannot give rise to other precursor cells.

B. Initial steps in blood cell formation (stem cells)

1. **PHSCs** (also known as **hemopoietic stem cells** [**HSCs**]) give rise to **multipotential hemopoietic stem cells** in the bone marrow. Although PHSCs cannot be recognized by their morphology, they *possess certain cell membrane markers* that assist in their recognition:
   a. **CD34** permits adherence of this cell to other cells as well as to the extracellular matrix.
   b. **CD59** inhibits the formation of the complement cascade known as membrane attack complex.
   c. **CD133** may help CD59 in performing its function.
   d. **Thy1** (thymocyte antigen 1) is believed to function in the adherence of the cell to the extracellular matrix and to bone marrow stromal cells.
   e. **C-kit receptor** (also known as **CD117)** acts as a receptor molecule for **stem cell factor** (also known as **C-kit ligand** and **steel factor**) and is *negative for other cell membrane markers*, which further assists in its recognition.
   f. **CD38** is responsible for the mechanism of intracellular Ca^{2+} ion regulation.
2. **Multipotential hemopoietic stem cells** are of two types: (1) **colony-forming unit—granulocyte, erythrocyte, monocyte, megakaryocyte** (**CFU-GEMM** also known as **common myeloid progenitor cells** [**GMP cells**]) and (2) **CFU—lymphocyte** (**CFU-Ly**, also known as **common lymphoid progenitor cells** [**CLP cells**]). These cells divide and differentiate in bone marrow to form **progenitor cells** (referred to as **lineage-restricted progenitors** by some authors).
   a. **CFU-GEMM** (**GMP cells**), the **myeloid stem cell**, is the multipotential stem cell that gives rise to erythrocytes, granulocytes, monocytes, and platelets. **Homeobox genes** are probably active in early differentiation; **Hox 2 genes** in the erythroid lines; and **Hox 1 genes** in granulocytes, monocytes, and platelets.
   b. **CFU-Ly** (**CLP cells**), the **lymphoid stem cell,** is the multipotential stem cell that gives rise to T and B lymphocytes and NK cells.

C. Erythrocyte formation (erythropoiesis)

begins with formation of two types of progenitor cells: 1. *burst-forming unit—erythroid (BFU-E)*, derived from CFU-GEMM (GMP) under the influence of erythropoietin, stem cell factor, IL-1, IL-3, and IL-4, and 2. *CFU—erythroid (CFU-E)*, which arises from BFU-E. Erythropoiesis yields about 2.5×10^{11} RBCs daily in an average adult (Table 5.6).

table 5.6 Number of Blood Cells and Platelets Formed By Average Adult per Day

Cell	Number Formed per Day
Erythrocytes	2.5×10^{11}
Neutrophils	800,000
Eosinophils	170,000
Basophils	60,000
Monocytes	10^{10}
Lymphocytes	10^{8}
Platelets	4×10^{11}

1. **Erythroid progenitor cells**
   a. **BFU-E** has a high rate of mitotic activity and responds to high concentrations of **erythropoietin**.
   b. **CFU-E** responds to low concentrations of erythropoietin and gives rise to the first histologically recognizable erythrocyte precursor, the **proerythroblast**.
2. **Erythrocyte precursor cells** include a series of cell types (the **erythroid series**) that differentiate sequentially to form mature erythrocytes (Table 5.7 and Fig. 5.5).

D. **Granulocyte formation begins with production of three unipotential or bipotential cells, all of which are descendants of *CFU-GEMM (GMP)*.** The process of forming CFU-GEMM from **PHSCs** requires high levels of **PU.1 transcription factor**, a protein that has an affinity for purine-rich segments of DNA present in the vicinity of promoter genes. By attaching to the purine-rich segment the promoter gene is activated and PHSCs differentiate into GEMM cells. Other cytokines (see Table 5.5), such as **granulocyte–monocyte CSF (GM-CSF), granulocyte CSF (G-CSF),** and **IL-3, IL-6,** and **IL-8,** are responsible for the formation of granulocytes. The additional presence of **IL-5** directs the differentiation toward the eosinophil line, whereas if IL-5 is not present the differentiation proceeds toward the formation of basophils. Granulocyte formation yields about 1 million granulocytes daily in a normal adult.

1. **Granulocyte progenitor** cells give rise to histologically identical **myeloblasts** and **promyelocytes** in all three cell lineages.
   a. **CFU—eosinophil** (**CFU-Eo**) is the progenitor of the **eosinophil** lineage.
   b. **CFU—basophil** (**CFU-Ba**) is the progenitor of the **basophil** lineage.
   c. **CFU—granulocyte–monocyte** (**CFU-GM**), the common progenitor of **neutrophils** and **monocytes,** gives rise to **CFU-G** (granulocyte, specifically neutrophil) and **CFU-M** (monocyte).

table 5.7 Selected Characteristics of Erythrocyte Precursor Cells

Characteristic	Proerythroblast	Basophilic Erythroblast	Polychromatophilic Erythroblast (Normoblast)	Orthochromatophilic Erythroblast	Reticulocyte
Nucleus shape	Round	Round	Round and small	Round	None
Color*	Burgundy red	Burgundy red	Dense blue	Dark, may be extruding	None
Chromatin network	Very fine	Fine	Coarse	Pyknotic	None
Number of nucleoli	3–5 (very pale gray)	1–2	None	None	None
Mitosis	Yes	Yes	Yes	No	No
Cytoplasmic color*	Pale gray with blue clumps	Grayish pink with intensely blue clumps	Yellowish pink with bluish background	Pink with trace of blue	Pink†
Hemoglobin	None (ferritin is present)	Some	Abundant	Abundant	Abundant

*Cells stained with Giemsa or Wright stain.
†Cells stained supravitally with brilliant cresyl blue display a reticulum.

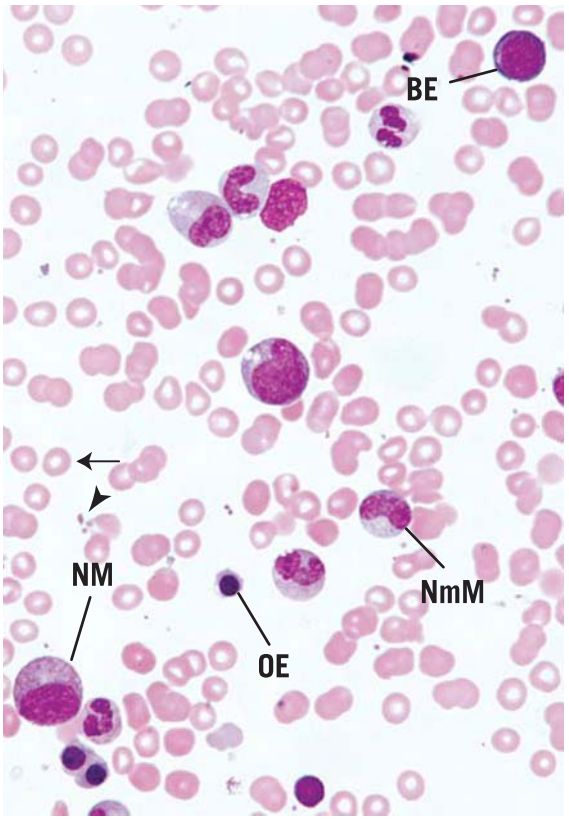


FIGURE 5.5. Light micrograph of a human bone marrow smear. Wright stain (×540). BE, basophilic erythroblast; NM, neutrophilic myelocyte; NmM, neutrophilic metamyelocyte; OE, orthochromatophilic erythroblast; *arrow*, erythrocyte; *arrowhead*, platelet.

2. **Granulocyte precursor cells** are histologically similar in the early stages of all three lineages (myeloblasts and promyelocytes). They develop characteristic granules unique to each cell type during the myelocyte stage and a distinctive nuclear shape during the stab (band) stage (Table 5.8; also see Fig. 5.5).
3. It should be noted that under the influence of **stem cell factor** the precursor cell, **myeloblast**, gives rise to **mast cells**.

E. Monocyte formation (CFU-M) begins with the common progenitor CFU–neutrophil–monocyte (CFU-NM) and involves only two precursor cells: *monoblasts* and *promonocytes*. Monocyte formation yields about 10 trillion monocytes daily in a normal adult.

1. **Promonocytes** are reportedly large cells (16–18 μm in diameter) that contain a kidney-shaped acentric nucleus, numerous azurophilic granules, an extensive rough endoplasmic reticulum (RER) and Golgi complex, and many mitochondria. They undergo cell division and subsequently develop into **monocytes**.
2. **Monocytes** leave the bone marrow to enter the circulation. From the bloodstream, they enter connective tissue, where they differentiate into **macrophages**, **antigen-presenting cells**, **osteoclasts**, **microglia**, and **dendritic cells**.

F. Platelet formation begins with the progenitor *CFU-Meg* (also known as *megakaryocyte-committed progenitor cells* [*MKP cells*]), which arises from CFU-GEMM and involves a single precursor cell (the *megakaryoblast*), and the mature *megakaryocyte*, which remains in the bone marrow and sheds platelets into the sinusoids.

1. **Megakaryoblasts**
   - **a.** These large cells (25–40 μm in diameter) have a single large nucleus that may be indented or lobed and displays a fine chromatin network.
   - **b.** Their basophilic, nongranular cytoplasm contains large mitochondria, many polysomes, some RER, and a large Golgi complex.

table 5.8 Selected Characteristics of Neutrophil Precursor Cells

Characteristic	Myeloblast	Promyelocyte	Neutrophilic Myelocyte	Neutrophilic Metamyelocyte	Neutrophilic Stab Cell
Cell diameter (μm)	12–14	16–24	10–12	10–12	11–12
Nucleus shape	Large, round	Large, round	Flat (acentric)	Kidney (acentric)	Horseshoe
Color*	Reddish blue	Reddish blue	Blue to dark blue	Dark blue	Dark blue
Chromatin network	Very fine	Fine	Coarse	Very coarse	Very coarse
Number of nucleoli	Two of three (pale gray)	One or two (pale gray)	Perhaps one	None	None
Mitosis	Yes	Yes	Yes	No	No
Cytoplasmic appearance*	Blue clumps in pale blue background, cytoplasmic blebs at cell periphery	Bluish hue, no cytoplasmic blebs	Pale blue	Blue	Similar to mature neutrophils
Granules	None	Azurophilic	Azurophilic and specific	Azurophilic and specific	Azurophilic and specific

*Cells started with Giemsa or Wright stain.

c. Under the influence of the hormone **thrombopoietin**, megakaryoblasts divide endomitotically (i.e., no daughter cells are formed) and enlarge; the ploidy of the nucleus increases to as much as 64 N, giving rise to megakaryocytes.

2. **Megakaryocytes**
   a. These extremely large cells (40–100 μm in diameter) have a single large **polypoid** nucleus that is highly indented (see Fig. 5.4).
   b. They possess a well-developed Golgi complex associated with the formation of α-granules, lysosomes, and dense bodies (δ-granules); they also contain many mitochondria and an extensive RER.
   c. Megakaryocytes lie just outside the sinusoids in the bone marrow and form **platelet demarcation channels**, which fragment into proplatelets (clusters of adhering platelets) or single platelets that are released into the sinusoidal lumen.

G. **Lymphocyte formation (lymphopoiesis) begins with differentiation of *CFU-Ly* (*CLP*), the lymphoid stem cell, into the *immunoincompetent* progenitor cells *CFU-LyB* and *CFU-LyT***. This step requires the presence of medium concentrations of **transcription factor PU.1** as well as intranuclear **zinc finger transcription factors** such as the **Ikaros family of transcription factors**. These zinc finger proteins have protruding hairpin-like extensions, maintained by zinc and iron ions that fit into grooves in the promoter or other regulatory regions of the DNA molecule and, thereby, activate or inhibit a particular gene. (Note that zinc finger proteins bind not only to DNA but also to RNA, proteins, and lipids.) These prelymphocytes are processed and become mature immunocompetent cells.

1. **B lymphocyte (B-cell) maturation**
   a. Requires the presence of **Pax5 transcription factor** and **IL-7**
   b. Pre-B lymphocytes acquire cell surface markers, including membrane-bound **antibodies**, which confer **immunocompetence**.
   c. In mammals, B-cell maturation occurs in the bone marrow, whereas in birds, it occurs in the bursa of Fabricius (hence, **B** lymphocytes).
2. **T lymphocyte (T-cell) maturation**
   a. Requires the presence of **GATA-3 transcription factor** and **IL-7**
   b. Progenitor T lymphocytes migrate to the **thymic cortex**, where they acquire cell surface markers, including **T-cell receptors**, which confer **immunocompetence**.
   c. Most of the newly formed T lymphocytes are destroyed in the cortex of the thymus and do not enter into circulation.
3. **Mature B and T lymphocytes** leave the bone marrow and thymus, respectively, and circulate to peripheral organs (e.g., the lymph nodes and spleen) to establish **clones** of immunocompetent lymphocytes (see Chapter 10).

Review Test

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or completions of the statement. Select the ONE lettered answer that is BEST in each case.

1. A 4-year-old boy is taken by his parents to the pediatrician because of vomiting, headaches, and tenderness in the bones of his arms and legs. On palpation, the physician notes that many lymph nodes are enlarged, as is the liver. The pediatrician should order a complete blood count in order to determine whether or not the child may have

(A) chronic leukemia.
(B) infectious mononucleosis.
(C) von Willebrand disease.
(D) acute leukemia.
(E) pernicious anemia.

Questions 2 and 3 refer to the following scenario:

A female patient presents to the emergency room with a chief complaint of dark patches on her tongue; multiple small, red dot-like structures on her skin; and a large, bluish bruise developing after she bumped into the back of a wooden chair.

2. What should the physician suspect?

(A) Hemophilia
(B) Epstein–Barr viral infection
(C) Thrombocytopenia
(D) Allergic response
(E) Iron deficiency anemia

3. What is one of the first tests that the doctor should order?

(A) Genetic analysis
(B) IgE serum levels
(C) Computed axial tomography scan
(D) Magnetic resonance imaging
(E) Complete blood count

Questions 4 and 5 refer to the following scenario:

A patient who immigrated to the United States from Africa a few months ago presents with an aggressive tumor of B lymphocytes in the orofacial region.

4. What should the physician suspect?

(A) Cytomegalovirus infection
(B) Epstein–Barr virus infection
(C) Infectious mononucleosis
(D) Endemic Burkitt lymphoma
(E) Acute leukemia

5. Where would the physician expect to find additional tumors?

(A) Liver
(B) Spleen
(C) Bone marrow
(D) Lungs
(E) Brain

Questions 6 and 7 refer to the following scenario:

A female patient with a bleeding disorder has exceptionally large platelets.

6. What is her disease?

(A) Bernard–Soulier syndrome
(B) Glanzmann thrombasthenia
(C) von Willebrand disease
(D) Hemophilia A
(E) Thrombopenia

7. What defect causes her disease?

(A) Inability to bind to von Willebrand factor
(B) Inability to bind to fibrinogen
(C) Increased von Willebrand factor levels
(D) Decreased factor VIII levels
(E) Decreased platelet levels

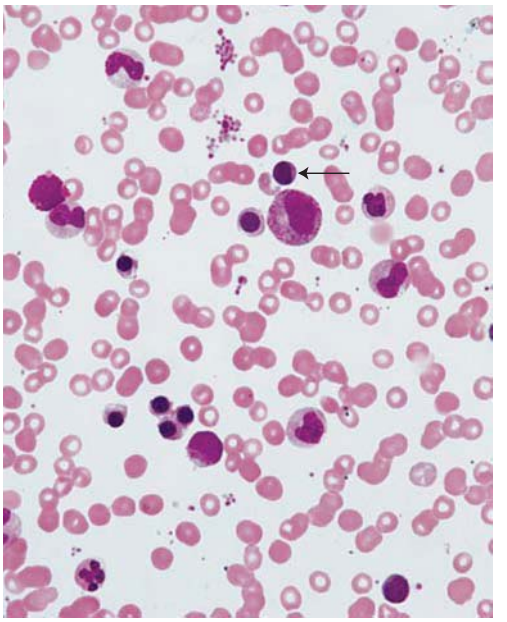
8. A pediatrician suspects that her male patient has leukemia. What results would she expect in a complete blood count?

(A) High platelet count
(B) Increased number of mature cells
(C) Increased number of immature cells
(D) Low WBC count
(E) Increase in RBC level

9. A universal donor can accept blood from an individual with which blood type?

(A) A
(B) B
(C) AB
(D) O
(E) Rh^+

10. This question is based on the accompanying light micrograph.



What is the cell at the tip of the arrow?

(A) Lymphocyte
(B) Orthochromatophilic erythroblast
(C) Polychromatophilic erythroblast
(D) Neutrophilic stab cell
(E) Monocyte

Answers and Explanations

1. **D. Acute leukemia** is a disease of children with symptoms that include headaches; vomiting; swollen lymph nodes, liver, and spleen; and the sensation of tenderness in bones. Chronic leukemia is a disease that usually affects adults. von Willebrand disease is a coagulation disorder and does not have the same symptoms as acute leukemia. Infectious mononucleosis affects mostly young adults of high school and college age. Pernicious anemia is caused by vitamin B deficiency, and its symptoms do not resemble those of acute leukemia.
2. **C.** The physician should suspect thrombocytopenia, a reduced level of platelets in the blood.
3. **E.** A complete blood count will determine if the clinician is correct in his suspicion of thrombocytopenia being the real culprit.
4. **D.** Because the patient lived in Africa and presents with an aggressive B-cell tumor in the orofacial region, the physician should suspect endemic Burkitt lymphoma. It is referred to as endemic because it is present in areas of the world where malaria is endemic.
5. **E.** Endemic Burkitt lymphoma tumors first appear in the orofacial region and spread to the breasts, ovaries, gastrointestinal tract, and the brain.
6. **A.** Bernard–Soulier syndrome is characterized by the presence of excessively large platelets whose membranes have reduced GPIb integrin levels.
7. **A.** Because these platelets have low levels of GPIb integrin in their membranes, they are unable to bind to von Willebrand factor.
8. **C.** Acute leukemias usually occur in children and are characterized by many immature cells, high WBC count, depressed RBC levels, and a low platelet count.
9. **D.** A universal donor's blood type is O; therefore, he or she can accept blood only from an individual whose blood type is O.
10. **A.** The cell at the tip of the arrow is a lymphocyte as is evident by its large, acentric nucleus and the scant rim of cytoplasm.

chapter 6

Cartilage and Bone

I. OVERVIEW—CARTILAGE

Cartilage, an **avascular** specialized **connective tissue**, has a **firm extracellular matrix** (**ECM**) that is less pliable than the ECM of connective tissue proper; is more resistant to mechanical pressure; and has cells known as **chondrocytes** housed in **lacunae**, small cavities in the matrix. Surrounding the cartilage is a dense irregular connective tissue, the **perichondrium** housing mostly fibroblasts; located in the inner layer of the perichondrium are the cells responsible for forming cartilage, **chondroblasts** and **chondrogenic cells**. Cartilage **functions** primarily to support soft tissues and assists in the development and growth of long bones. The three types of cartilage—**hyaline cartilage**, **elastic cartilage**, and **fibrocartilage**—vary in certain matrix components (Table 6.1).

A. Hyaline cartilage (Figs. 6.1 and 6.2; Table 6.1) is the most abundant cartilage in the body, and it also serves as a temporary skeleton in the fetus until it is *replaced* by bone.

1. Structure

a. Matrix. The matrix, composed of an amorphous ground substance, is rich in **proteoglycan aggregates** and the glycoprotein **chondronectin** as well as **type II collagen** (Table 6.1; also see Table 2.2). The matrix that immediately surrounds the lacunae is called the **territorial matrix**. This part of the matrix is poor in collagen but rich in proteoglycans, and it stains more deeply than does the bulk of the matrix, known as **interterritorial matrix**.

b. Perichondrium is a layer of dense, irregular connective tissue that surrounds hyaline cartilage except at articular surfaces.

table 6.1 Cartilage Types, Characteristics, and Locations

Type of Cartilage	Identifying Characteristics	Perichondrium	Location
Hyaline	Type II collagen, basophilic matrix, chondrocytes usually arranged in groups (isogenous groups)	Perichondrium usually present except on articular surfaces	Articular ends of long bones, nose, larynx, trachea, bronchi, ventral ends of ribs, template for endochondral bone formation
Elastic	Type II collagen; elastic fibers	Perichondrium present	Pinna of ear, auditory canal and tube, epiglottis, some laryngeal cartilages
Fibrocartilage	Type I collagen, acidophilic matrix, chondrocytes arranged in parallel rows between bundles of collagen, always associated with dense collagenous connective tissue and/or hyaline cartilage	Perichondrium absent	Intervertebral disks, articular disks, pubic symphysis, insertion of tendons, meniscus of knee

Adapted with permission from Gartner LP, Hiatt JL. *Color Textbook of Histology*. Philadelphia, PA: Saunders; 1997:132.

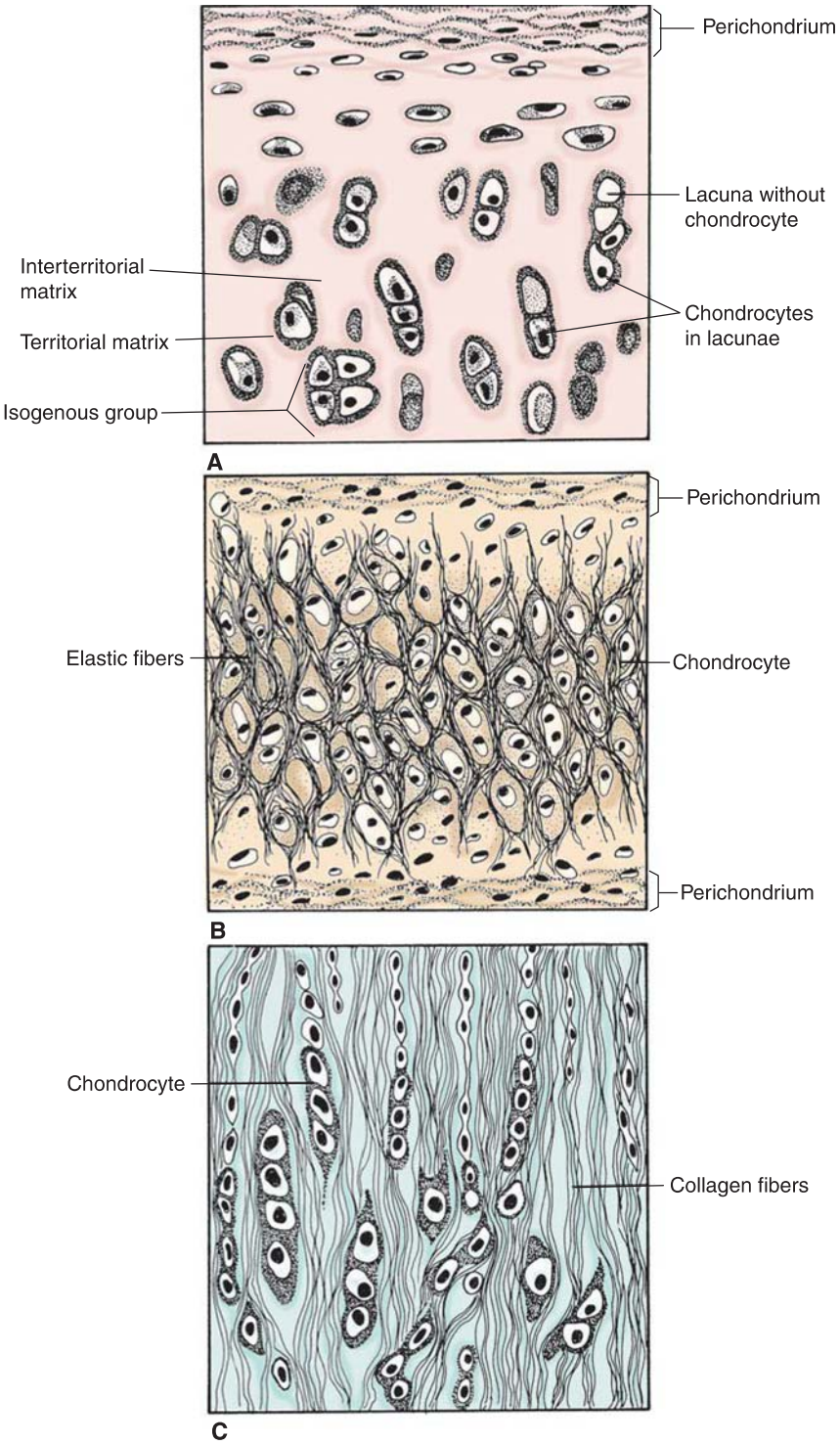


FIGURE 6.1. The three types of cartilage. **A.** Hyaline cartilage. **B.** Elastic cartilage. **C.** Fibrocartilage. (Reprinted with permission from Borysenko M, Berringer T. *Functional Histology*. 2nd ed. Boston, MA: Little Brown and Co.; 1984:102.)

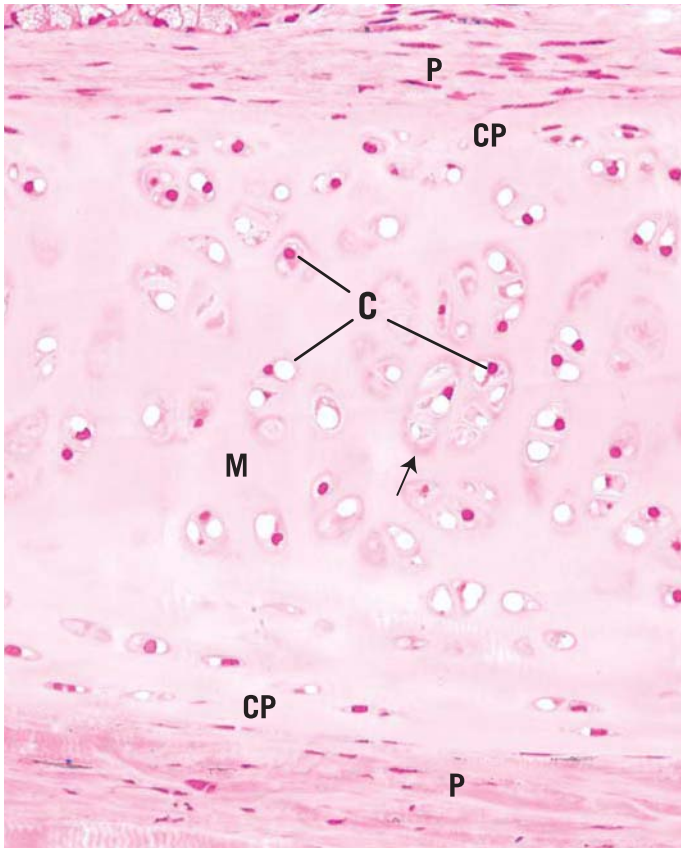


FIGURE 6.2. Light micrograph of hyaline cartilage of the monkey trachea (×270). Observe the chondrocytes (C), perichondrium (P), chondrogenic perichondrium (CP), matrix (M), and the lacuna (*arrow*).

(1) It consists of an **outer fibrous layer** containing **type I collagen**, fibroblasts, and blood vessels and an **inner cellular layer** containing **chondrogenic cells** and **chondroblasts**.
(2) It **provides the nearest blood supply** to the avascular cartilaginous tissue.

c. **Chondrogenic cells** are of two types: those present in mesenchymal connective tissue where cartilage is being formed and those located within the inner layer of the perichondrium. Chondrogenic cells of mesenchymal connective tissue give rise to chondrocytes directly, whereas chondrogenic cells of the inner layer of the perichondrium differentiate into chondroblasts.

d. **Chondroblasts** manufacture the cartilage matrix through which nutrients and waste materials pass to and from the cells, respectively. These cells contain an extensive Golgi complex, abundant rough endoplasmic reticulum (RER), lipid droplets, and glycogen. Once these cells become totally enveloped by matrix, they are referred to as **chondrocytes** (see Figs. 6.1 and 6.2).

CLINICAL CONSIDERATIONS

Mesenchymal cells can be induced to become secreting chondroblasts in the proper environment, but if removed and grown as a monolayer in a low-density substrate, they will discontinue secreting cartilage matrix, become fibroblast-like, and secrete type I rather than type II collagen.

Degeneration of hyaline cartilage occurs when chondrocytes undergo hypertrophy and die and the matrix becomes calcified, a process that becomes more frequent with age. Degeneration of hyaline cartilage is also a normal part of endochondral bone formation.

table 6.2 Effects of Hormones and Vitamins on Hyaline Cartilage

Hormones	Function
Thyroxine, testosterone, somatotropin	Stimulate cartilage histogenesis
Cortisone, hydrocortisone, estradiol	Inhibit cartilage histogenesis
Vitamins	
Hypovitaminosis A	Diminishes thickness of epiphyseal plates
Hypervitaminosis A	Accelerates ossification of epiphyseal plates
Hypovitaminosis C	Stops matrix production, distorts cartilage columns in epiphyseal plates; scurvy develops
Hypovitaminasis D	Deficient absorption of calcium and phosphorus: epiphyseal cartilage cells proliferate, but matrix fails to calcify, and growing bones deformed; rickets develops

e. **Chondrocytes** are mature cartilage cells housed within **lacunae** in the matrix. Chondrocytes located **near the perichondrium** are ovoid and positioned with their longitudinal axis parallel to the cartilage surface. Those located **deeper** in the matrix are more nearly spherical and may occur in groups of four to eight cells (**isogenous groups**) within a single lacuna.

2. **Histogenesis of hyaline cartilage** is similar to that of elastic cartilage and is affected by certain hormones and vitamins (Table 6.2). It occurs by the following two processes:
   a. **Interstitial growth** results from cell **division of preexisting chondrocytes**, forming isogenous groups. Each cell of the isogenous group secretes matrix, pushing the cells of the group away from each other and each cell will eventually have its own lacuna. This type of growth occurs only during the early stages of cartilage formation and in articular cartilage and the epiphyseal plates of long bones.
   b. **Appositional growth** results from differentiation of chondrogenic cells in the perichondrium. This type of growth results in the formation of chondroblasts and/or new chondrocytes, which elaborate a new layer of cartilage matrix at the periphery.

CLINICAL CONSIDERATIONS

One of the processes of aging is the degeneration of hyaline cartilage, especially at the articulating surfaces of the number of bony joints. Over time, this causes joint pain, redness, swelling, and stiffness and restricts joint mobility, a condition known as **arthritis.**

Osteoarthritis occurs more frequently in women than in men and affects about 21 million middle-aged and older individuals in the United States. It is usually caused by wear and tear on the synovial joint, where the hyaline cartilage is worn away resulting in bone grinding on bone. Other causes include joint injury or infection within the joint. The symptoms of osteoarthritis include joint pain, stiffness when getting out of bed or after sitting for a longer period of time, reduction in the range of motion, compensatory change in the normal gait, and swelling of the joint.

Rheumatoid arthritis is a very severe form of arthritis, in which the immune system attacks the joint including the cartilage, bone, and the synovial membrane. If left untreated, it may destroy the joint including the cartilage and the bone.

B. Elastic cartilage **(Fig. 6.1; Table 6.1) possesses a perichondrium and is nearly identical to hyaline cartilage except for a network of elastic fibers, which impart a *yellowish* color to it on gross observation.** Although it contains type II collagen, it is less prone to degeneration than hyaline cartilage and does not calcify as much with aging. It is located in areas where **flexible support** is required. Elastic cartilage exists as the cartilage of the auditory tube, external ear, and epiglottis.

C. Fibrocartilage **(Fig. 6.1; Table 6.1) *lacks* an identifiable perichondrium.** It is characterized by alternating rows of fibroblast-derived chondrocytes surrounded by scant matrix and thick parallel bundles of **type I collagen** fibers. Fibrocartilage is located in areas where **support and tensile strength** are required and where tissues are exposed to compressive and shear forces, such as in the intervertebral disks, menisci of the knees, sternoclavicular joints, and the pubic symphysis.

II. OVERVIEW—BONE

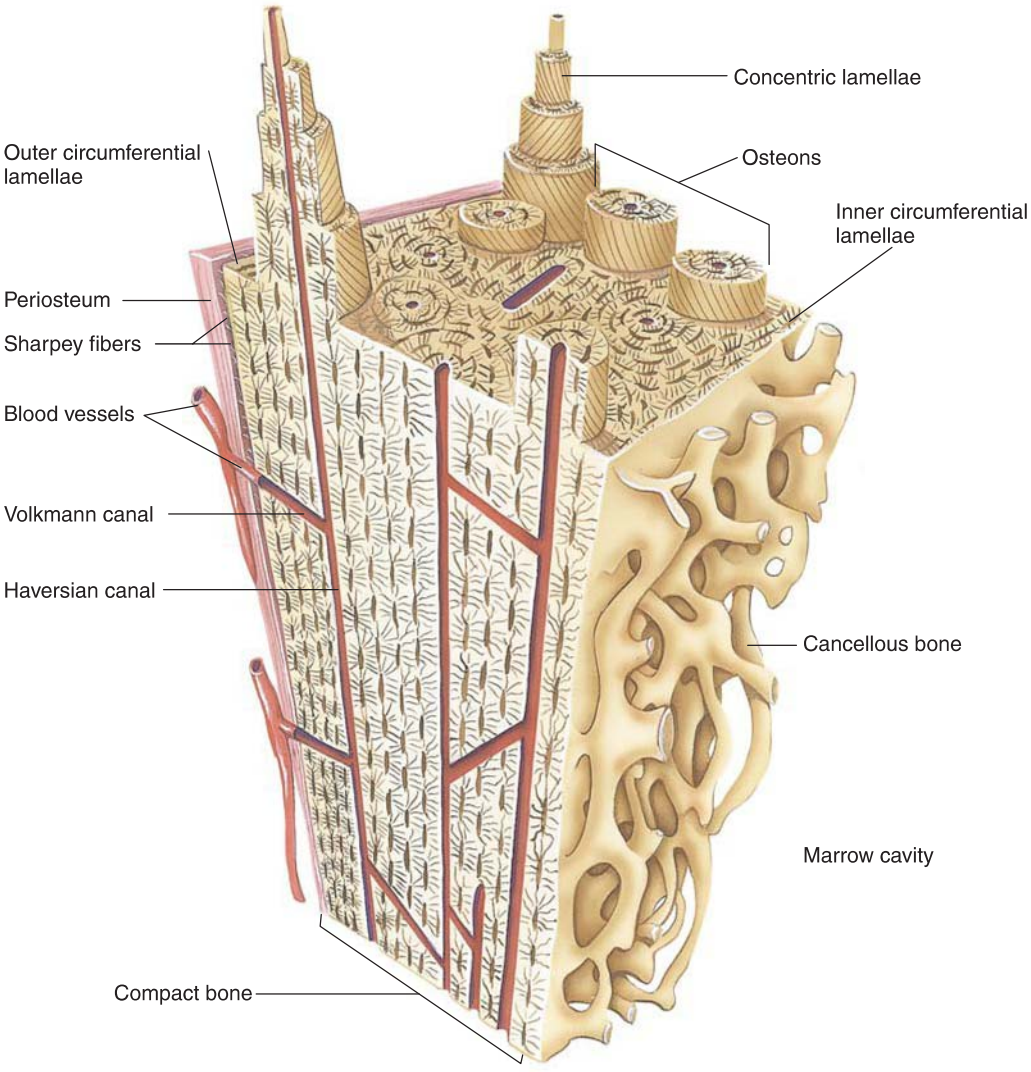
Bone is the primary constituent of the adult skeleton. It is a specialized type of connective tissue with a calcified extracellular matrix (ECM) in which characteristic cells are embedded. Bone functions to support and protect vital organs and fleshy structures, as a hemopoiesis organ, and to provide a storage site for phosphate and calcium (bone contains about 99% of the body's calcium). Secondarily, it functions to regulate blood calcium levels via input from two separate nonbony sources. Parathyroid hormone (PTH) from the parathyroid gland acts to increase calcium levels in the blood, whereas calcitonin secreted by the parafollicular cells of the thyroid gland decreases calcium levels in the blood. Thus, the activities of these two hormones on calcium levels in bone are responsible for maintaining the proper blood calcium level. Bone is also a dynamic tissue that constantly undergoes changes in shape, such that applied pressure results in bone *resorption*, whereas applied tension results in bone *formation*.

A. Structure

1. **Bone matrix**
   a. The **inorganic (calcified) portion of the bone matrix** (about 65% of the dry weight) is composed of calcium, phosphate, bicarbonate, citrate, magnesium, potassium, and sodium. It consists primarily of **hydroxyapatite crystals**, which have the composition $Ca_{10}(PO_4)_6(OH)_2$.
   b. The **organic portion of the bone matrix** (about 35% of the dry weight) consists primarily of **type I collagen** (95%) and a minor contribution of **type V collagen**. It has a ground substance that contains **chondroitin sulfate**, **keratan sulfate**, and **hyaluronic acid** as well as the glycoproteins **osteocalcin**, **osteopontin**, and **bone sialoprotein**.
      (1) **Osteocalcin**, **osteopontin**, and **bone sialoprotein** bind to hydroxyapatite but osteopontin and bone sialoprotein also bind to integrins on osteoblasts and osteoclasts facilitating the adherence of these cells to the bone matrix. Additional cytokines, growth hormones, and bone morphogenic proteins (BMPs) contribute to the bone matrix.
2. The **periosteum**, a layer of **noncalcified** dense irregular collagenous connective tissue covering bone on its **external** surfaces (except at synovial articulations and muscle attachments), functions to distribute blood vessels to bone. It is composed of an outer dense **fibrous** collagenous layer and an inner cellular **osteoprogenitor** (**osteogenic**) layer. **Sharpey fibers** (type I collagen) attach the periosteum to the bone surface (Fig. 6.3).
3. The **endosteum** is a thin specialized connective tissue that lines the **marrow cavities** and supplies **osteoprogenitor cells** and **osteoblasts** for bone growth and repair.

B. Bone cells

1. **Osteoprogenitor cells**
   a. These spindle-shaped cells, derived from embryonic mesenchyme, are located in the **periosteum** and the **endosteum**. They persist throughout life as stem cells that can be activated as necessary to repair bone.
   b. Under normal oxygen tension, they can differentiate into **osteoblasts**; however, at **low** oxygen tensions, they may change into **chondrogenic cells**.
2. **Osteoblasts**
   a. **Osteoblasts** are derived from osteoprogenitor cells under the influence of members of the **BMP family** and also **transforming growth factor-β**. Osteoblasts are responsible for the synthesis of organic protein components of bone matrix, including type I (and a small amount of type V) collagen, proteoglycans, and glycoproteins, which they secrete as **osteoid** (**uncalcified bone matrix**). Osteoid is mineralized under the influence of and control by the osteoblasts. Additionally, osteoblasts produce a number of cytokines (Table 6.3) such as macrophage colony-stimulating factor (**M-CSF**), a receptor for the activation of nuclear factor κB ligand (**RANKL**), **osteoprotegerin** (**OPG**), **osteocalcin** (for bone mineralization), **osteopontin** (for formation of sealing zone between osteoclasts and the subosteoclastic compartment), **osteonectin** (related to bone mineralization), and **bone sialoprotein** (binding osteoblasts to ECM). They also possess PTH receptors on their cell membrane.



Compact Bone

Compact bone is surrounded by dense irregular collagenous connective tissue, the **periosteum**, which is attached to the **outer circumferential lamellae** by **Sharpey fibers**. Blood vessels of the periosteum enter the bone via larger nutrient canals or small **Volkmann canals**, which not only convey blood vessels to the **Haversian canals** of **osteons** but also interconnect adjacent Haversian canals. Each osteon is composed of concentric lamellae of bone whose collagen fibers are arranged so that they are perpendicular to those of contiguous lamellae. The **inner circumferential lamellae** are lined by endosteal lined cancellous bone that protrudes into the marrow cavity.

FIGURE 6.3. Histologic aspects of a long bone. (Reprinted with permission from Gartner LP. *Color Atlas and Text of Histology*. 7th ed. Baltimore, MD: Wolters Kluwer Health; 2018:96.)

b. On bony surfaces, they appear as a layer of flat to high cuboidal, basophilic cells that become taller and increase their RER and Golgi as they secrete the organic matrix of bone (Fig. 6.4).

c. They possess cytoplasmic processes with which they contact the processes of other osteoblasts and osteocytes and form **gap junctions**.

d. As they secrete matrix around themselves, osteoblasts become entrapped in **lacunae** but maintain contact with other cells via their cytoplasmic processes. Entrapped osteoblasts are known as osteocytes.

table 6.3 Function of Cytokines Released by Osteoblasts

Cytokine	Function
BMP	Induces osteoprogenitor cells to differentiate into osteoblasts
TGF-α	Induces osteoprogenitor cells to differentiate into osteoblasts
RANKL	Induces preosteoclasts to differentiate into osteoclasts
M-CSF	Stimulates the formation of osteoclast precursors and to express RANK on their surface
Alkaline phosphatase	Promotes mineralization of bone
IGF-1	Promotes bone formation
PTH receptors	Parathyroid hormone binds to PTH receptors and promotes the RANKL secretion by osteoblasts
Osteocalcin	Promotes bone mineralization
Osteonectin	Promotes binding of calcium hydroxyl apatite crystals to type I collagen
Osteoclast-stimulating factor	Activates osteoclasts to resorb bone
Osteopontin	Assists osteoclast attachment to bone surface—sealing zone
Bone sialoprotein	Aids osteoblasts in adhering to bone matrix
Osteoprotegerin	Binds to RANKL thereby inhibiting osteoclast formation
Interleukin-1	Promotes proliferation of osteoclast precursors
Interleukin-6	Promotes recruitment and differentiation of osteoclasts

BMP, bone morphogenic protein; IGF-1, insulin-like growth factor-1; M-CSF, macrophage colony-stimulating factor; PTH receptors, parathyroid hormone receptors; RANK, receptor for the activation of nuclear factor κB; RANKL, receptor for the activation of nuclear factor κB ligand; TGF-α, transforming growth factor-α.

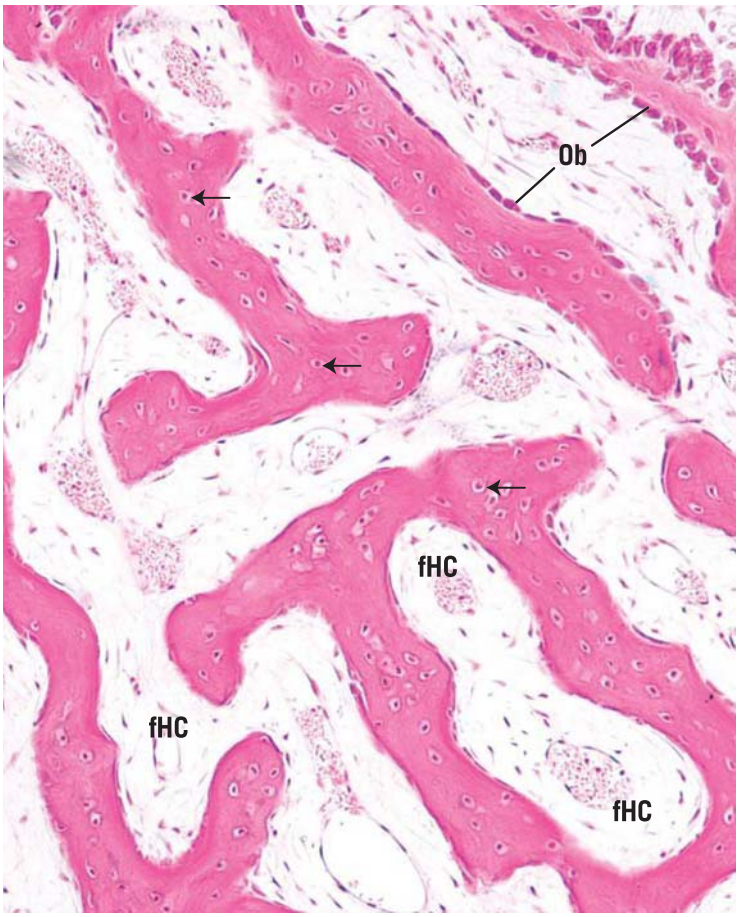


FIGURE 6.4. Light micrograph of membranous bone formation (×132). Observe the forming haversian canals (fHC), osteoblasts (Ob), and osteocytes (*arrows*).

3. **Osteocytes** (Figs. 6.5 and 6.6)
   a. Osteocytes, **mature bone cells** housed in their own lacunae, contain abundant heterochromatin, a paucity of RER, and a small Golgi complex. They have narrow cytoplasmic processes that extend through **canaliculi** in the calcified matrix and are nourished and maintained by nutrients, metabolites, and signal molecules carried by the extracellular fluid that flows through the lacunae and canaliculi. In addition, calcium released from bone enters the extracellular fluid located within these spaces.
   b. Osteocytes maintain communication with each other via **gap junctions** between their processes.
4. **Osteoclasts**
   a. **Osteoclasts** are large, motile, multinucleated cells (up to 50 nuclei) that resorb bone, a process known as **osteolysis** (Fig. 6.7). They are derived from cells of the **mononuclear-phagocyte system**, blood-borne **monocytes** that enter the connective tissue spaces and there they differentiate into various types of macrophages and osteoclasts.
      (1) Osteoclasts possess colony-stimulating factor-1 receptor, calcitonin receptor, and RANK (nuclear factor κB) on their cell membrane and they reside in depressions known as **Howship lacunae** (**resorption bays**), which represent areas from which they resorbed bone.
      (2) Five osteoblast-derived cytokines stimulate osteoclast formation and activity.
         (a) **M-CSF** stimulates osteoclast precursors (macrophages) to undergo mitosis.
         (b) **Interleukin-6** (**IL-6**) promotes recruitment and differentiation of osteoclasts.

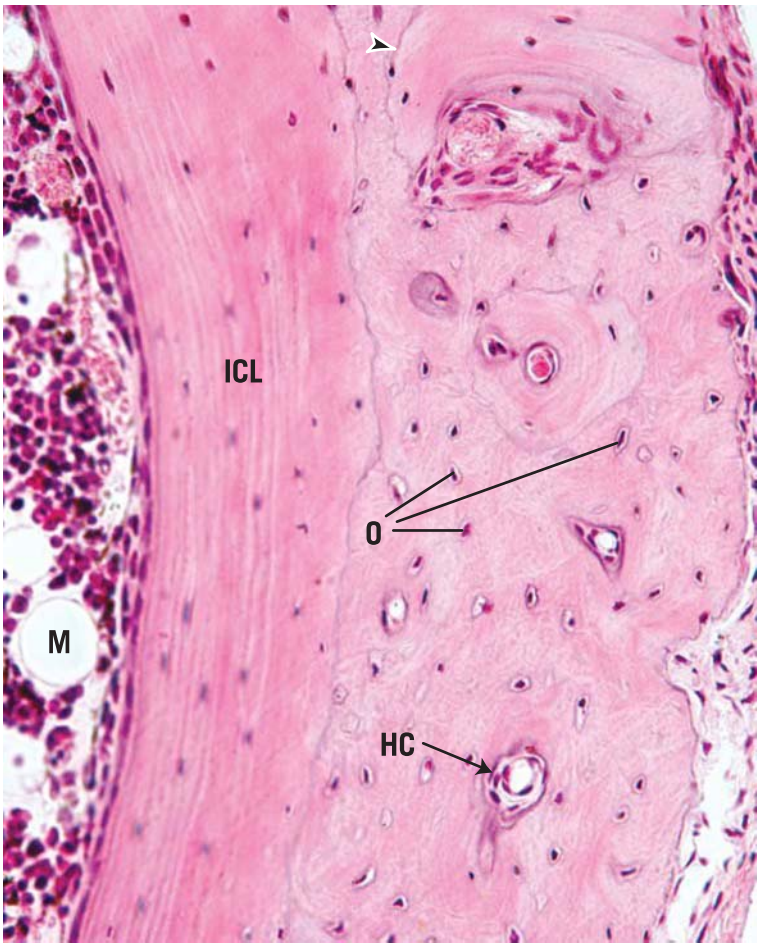


FIGURE 6.5. Light micrograph of bone and bone marrow from the rib (×270). M, bone marrow; ICL, inner circumferential lamellae; O, osteocytes; HC, haversian canal; arrowhead, cementing line.

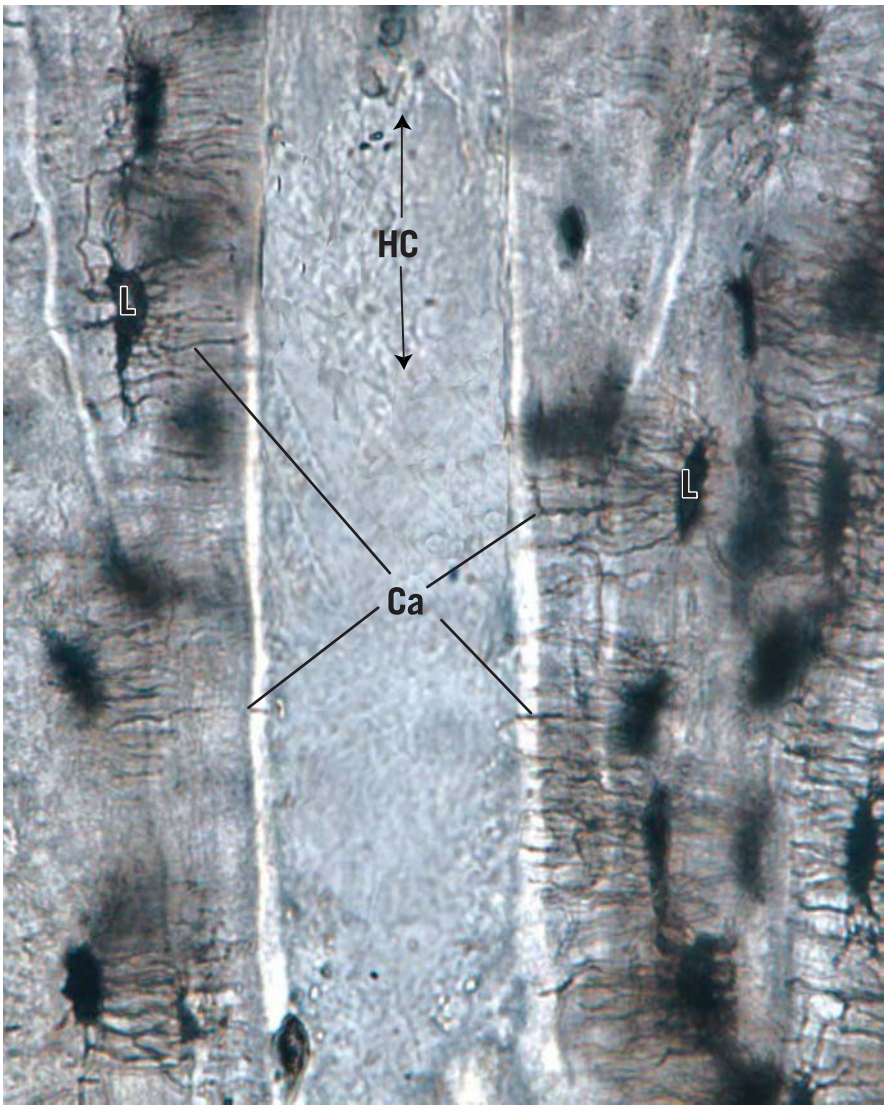


FIGURE 6.6. This longitudinal view of a high magnification of a ground section of compact bone displays lamellae of bone and their lacunae (L) with canaliculi (Ca) leading into the haversian canal (HC).

(c) **RANKL** binds to the osteoclast precursor, inducing it to differentiate into the multinucleated osteoclast, thus activating it to commence bone resorption.
(d) **Osteoclast-stimulating factor** (**OSF**) stimulates osteoclasts to resorb bone.
(e) **OPG**, a member of the **tumor necrosis factor receptor** family produced by osteoblasts and other cells, prevents RANKL from binding to the macrophage, thus inhibiting osteoclast formation.

b. Osteoclasts activated by **OSF** display four regions (Fig. 6.7).
(1) The **basal zone** is that part of the osteoclast housing most of the organelles and is the farthest from the subosteoclastic compartment.
(2) The **ruffled border** is the site of active bone resorption. It is composed of irregular fingerlike cytoplasmic projections extending into the **subosteoclastic compartment**, a slight depression that deepens as the osteoclast resorbs bone and then that depression is referred to as a **Howship lacuna**. The ruffled border of an inactive osteoclast is collapsed as the cell is in a resting stage.

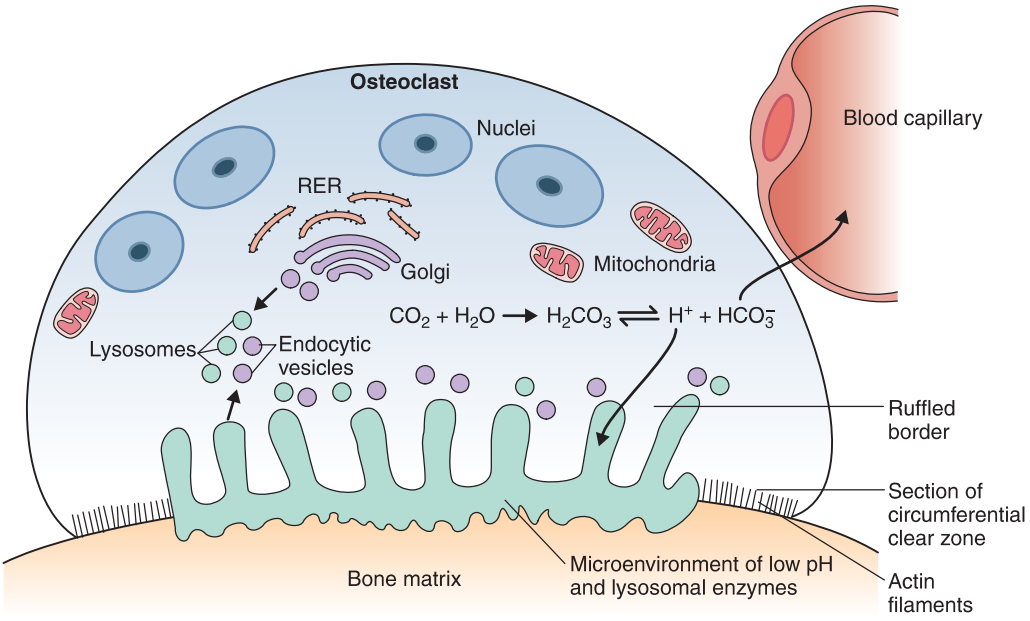


FIGURE 6.7. Osteoclastic function. The four regions of the osteoclast are demonstrated in this diagram. The clear zone and the ruffled border are labeled. Directly above the ruffled border is the vesicular zone, characterized by the presence of numerous vesicles, and the remainder of the cell, housing the nuclei and the organelles, is the basal zone. RER, rough endoplasmic reticulum.

(3) The **clear zone** surrounds the ruffled border. It contains actin filaments at the periphery that help osteoclasts maintain contact with the bony surface. This isolates and seals the region of osteolytic activity. Further, **osteopontin**, secreted by osteoblasts, is used to seal the zone between osteoclasts and the subosteoclastic compartment.

(4) The **vesicular zone** contains exocytotic vesicles that transfer lysosomal enzymes to Howship lacunae and endocytotic vesicles that transfer degraded bone products from Howship lacunae to the interior of the cell.

CLINICAL CONSIDERATIONS

Osteopetrosis, unlike osteoporosis, is a genetic disorder affecting osteoclasts so that they do not possess ruffled borders; therefore, these osteoclasts cannot resorb bone, which creates an imbalance between bone formation and bone resorption. Thus, persons with osteopetrosis display increased bone density. This condition leads to anemia, because of decreased marrow space, blindness, deafness, and damage to the cranial nerves as the foramina of the skull become narrow and impinge on the nerves.

c. Bone resorption (Fig. 6.7) involves the following events:

(1) Osteoclasts secrete H^+ and Cl^- ions into the subosteoclastic compartment where they combine to form **hydrochloric acid**, which decalcifies the surface layer of bone exposing its organic constituents.

(2) Acid hydrolases, proteolytic enzymes, and cathepsin K along with other collagenases **degrade the organic components** of the bone.

(3) Osteoclasts resorb the organic and inorganic residues of the bone matrix and release them into connective tissue capillaries.

(4) At the conclusion of the bone resorption function, osteoclasts undergo apoptosis.

(5) Increases in PTH stimulate osteoclastic activity thereby promoting bone resorption, whereas calcitonin, secreted by parafollicular cells of the thyroid gland, inhibits osteoclastic activity. However, PTH, under certain conditions may stimulate bone formation although the mechanism for this is not known.

C. Classification of bone is based on both gross and microscopic properties.

1. **Gross observation** (Fig. 6.3) of cross-sections of bone reveals two types:
   a. **Spongy** (**cancellous**) **bone** is composed of interconnected trabeculae. Bony trabeculae surround cavities filled with bone marrow. The trabeculae contain osteocytes in lacunae and are lined on all surfaces by a single layer of osteoblasts. Spongy bone is always surrounded by compact bone.
   b. **Compact** (**dense**) **bone** has no trabeculae or bone marrow cavities.
2. **Microscopic observation** of bone reveals two types:
   a. **Primary bone** (**immature bone**; **woven bone**; Fig. 6.4), the first compact bone produced during fetal development and during bone repair, has a low mineral content and has numerous osteocytes and large, irregularly arranged type I collagen bundles.
      (1) It is **remodeled** and **replaced by secondary bone** (except in a few places such as tooth sockets, near suture lines in skull bones, and at insertion sites of tendons).
   b. **Secondary bone** (**mature** or **lamellar bone**; Fig. 6.8), the compact bone of adults, has a calcified matrix arranged in **regular layers**, or **lamellae**, where each lamella is 3 to 7 μm thick.
      (1) It contains osteocytes in lacunae between, and occasionally within, lamellae.

D. Organization of lamellae in compact bone (e.g., diaphysis of long bones) is characteristic and consists of the following elements (Figs. 6.3, 6.5, and 6.8):

1. **Haversian systems** (**osteons**), long cylindrical structures that run approximately parallel to the long axis of the diaphysis, are composed of 4 to 20 lamellae surrounding a central **haversian**

FIGURE 6.8. Light micrograph of ground bone (×132). Observe the haversian canal (HC), cementing line (CL), interstitial lamellae (IL), Volkmann canal (VC), and osteocytes within lamellae (*arrows*).

canal, which contains blood vessels, nerves, and loose connective tissue. They are lined by osteoprogenitor cells and osteoblasts.

a. Each haversian system is often surrounded by an amorphous **cementing substance**.
b. Haversian canals are interconnected by **Volkmann canals**, which also connect to the periosteum and endosteum and **carry the neurovascular supply**.

2. **Interstitial lamellae** are irregularly shaped lamellae between haversian systems that are remnants of older, remodeled haversian systems.
3. **Outer** and **inner circumferential lamellae** are located at the external and internal surfaces of the diaphysis, respectively (Figs. 6.3 and 6.5).
4. Osteocytes are housed in lacunae within and/or between lamellae; these cells receive their nutrients and dispose their waste products via narrow channels known as **canaliculi**, which eventually lead into haversian canals (Fig. 6.6).

E. Histogenesis of bone occurs by two processes, *intramembranous* and *endochondral bone formation*. Both processes produce bone that appears histologically identical. As bone is being formed it is also being resorbed and, in that fashion, remodeled, a process slower in secondary than in primary bone.

1. **Intramembranous bone formation** (Fig. 6.4) is the process by which most of the **flat bones** (e.g., parietal bones of the skull) are formed. It involves the following events:
   a. Mesenchymal cells, in the presence of a vascular zone, condense into **primary ossification centers**, differentiate into osteoblasts, and begin secreting **osteoid** in a rather haphazard manner, forming **primary bone**.
   b. As appositional bone growth continues and the osteoid calcifies, osteoblasts become trapped in their own matrix and become osteocytes. These centers of developing bone are called **trabeculae** (fused spicules).
   c. Fusion of the bony trabeculae produces **spongy bone** as blood vessels invade the area and other undifferentiated mesenchymal cells become hemopoietic cells forming blood cells of the bone marrow.
   d. The periosteum and endosteum develop from portions of the mesenchymal layer that do not undergo ossification.
   e. Mitotic activity of the mesenchymal cells gives rise to osteoprogenitor cells, which undergo cell division and form more osteoprogenitor cells or differentiate into osteoblasts within the inner layer of the developing periosteum.
   f. Finally, some of the intramembranous bone becomes remodeled into lamellar bone.
2. **Endochondral bone formation** (Fig. 6.9) is the process by which **long bones** are formed. It begins in a segment of **hyaline cartilage** that serves as a small **cartilage model** for the bone. The two stages of endochondral bone formation involve the development of primary and secondary centers of ossification.
   a. The **primary center of ossification** develops at the **midriff of the diaphysis** of the hyaline cartilage model containing type II collagen by the following sequence of events:
      (1) Vascularization of this small region of the perichondrium increases the oxygen tension causing the transformation of **chondrogenic cells** to **osteoprogenitor cells**, which differentiate into osteoblasts. This region of the perichondrium is now called the **periosteum**.
      (2) Osteoblasts elaborate matrix deep to the periosteum and, via **intramembranous bone formation**, form the **subperiosteal bone collar**.
      (3) Chondrocytes within the core of the cartilaginous model undergo **hypertrophy** and degenerate, and their lacunae become confluent, forming large cavities that eventually become marrow spaces.
      (4) Osteoclasts create perforations in the bone collar that permit the **periosteal bud** (blood vessels, osteoprogenitor cells, and mesenchymal cells) to enter the newly formed spaces in the cartilaginous model. The cartilage that constitutes the walls of these spaces then becomes calcified.
      (5) Newly developed osteoblasts elaborate bone matrix that becomes calcified on the surface of the calcified cartilage, forming a **calcified cartilage–calcified bone complex**. In histologic sections, the calcified cartilage stains **basophilic**, whereas the calcified bone stains **acidophilic**.
      (6) The subperiosteal bone collar becomes thicker and elongates toward the epiphysis.

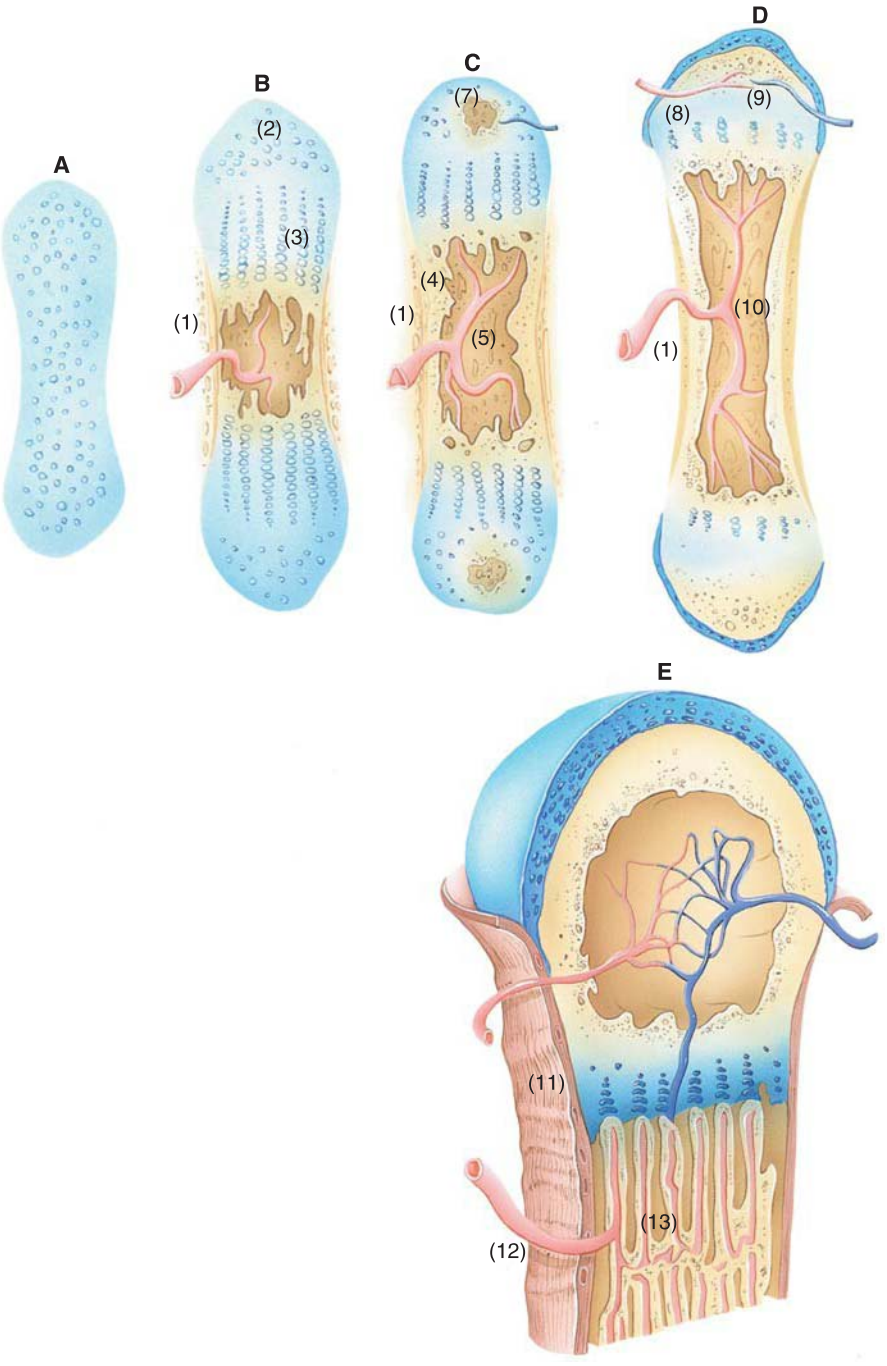


FIGURE 6.9. Endochondral bone formation. **A.** Endochondral bone formation requires the presence of a hyaline cartilage model. **B.** Vascularization of the perichondrium of the diaphysis (1) results in the transformation of chondrogenic cells to osteogenic cells, hence formation via intramembranous bone formation of a subperiosteal bone collar (1) that quickly becomes perforated by osteoclastic activity. Chondrocytes in the center of the cartilage hypertrophy (3) and their lacunae become confluent. **C.** The subperiosteal bone collar (1) increases in length and width. The confluent lacunae are invaded by the periosteal bud (4). Osteoclastic activity forms a primitive marrow cavity (5) whose walls are composed of calcified cartilage—calcified bone complex. The epiphyses display the beginning of secondary ossification centers (7). **D** and **E.** The subperiosteal bone collar (1) is now large enough to support the developing long bone, so that much of the cartilage has been resorbed except for the epiphyseal plate (8) and the covering of the epiphyses (9). Ossification in the epiphyses occurs from the center (10); thus, the vascular periosteum (11) does not cover the cartilaginous surface. Blood vessels (12) enter the epiphyses, without vascularizing the cartilage, to constitute the vascular network (13) around which spongy bone will form. (Reprinted with permission from Gartner LP. *Color Atlas of Histology*. 7th ed. Baltimore, MD: Wolters Kluwer; 2018:97.)

(7) Osteoclasts begin to resorb the calcified cartilage–calcified bone complex, thus enlarging the primitive marrow cavity.
(8) Repetition of this sequence of events results in bone formation spreading toward the **epiphyses**.

b. **Secondary centers of ossification** develop at the **epiphyses** in a sequence of events similar to that described for the primary center, except a bone collar is not formed.
(1) Development of these centers begins when osteoprogenitor cells, accompanied by vascular channels, invade the epiphysis and differentiate into osteoblasts, which elaborate bone matrix to replace the disintegrating cartilage. When the epiphyses are filled with bone tissue, cartilage remains in two areas, the articular surfaces and the epiphyseal plates.
(2) Articular cartilage persists and does not contribute to bone formation.
(3) Epiphyseal plates continue to grow by adding new cartilage at the epiphyseal end while being replaced with bone at the diaphyseal end (lengthening the bone).
(4) Ossification of the epiphyseal plates and cessation of growth occur at about 20 years of age.

3. **Zones of the epiphyseal plates** are histologically distinctive and arranged in the following order:
a. The **zone of reserve** cartilage is at the epiphyseal side of the plate. It possesses small, randomly arranged inactive chondrocytes.
b. The **zone of proliferation** (of chondrocytes) is a region of rapid mitotic divisions giving rise to rows of isogenous cell groups.
c. The **zone of cell hypertrophy and maturation** is the region where the chondrocytes are greatly enlarged.
d. The **zone of calcification** is the region where hypertrophied chondrocytes die and the cartilage becomes calcified.
e. The **zone of ossification** is the area where newly formed osteoblasts elaborate bone matrix on the calcified cartilage, forming a calcified cartilage–calcified bone complex, which is resorbed and replaced by bone.

4. **Calcification** of bone is not clearly understood, however,
a. **Osteonectin**, **proteoglycans**, and **bone sialoprotein** are known to stimulate calcification.
b. Bone matrix contains high concentrations of calcium Ca^{2+} as well as a plethora of organic compounds and enzymes. The presence of osteocalcin and sialoproteins increases Ca^{2+} levels; osteoblasts secrete alkaline phosphatase, which cleaves phosphate groups from organophosphate compounds thus concentrating PO_4^{3-} ions. Small matrix vesicles are released by the osteoblasts into the bone matrix, which facilitate deposition of calcium phosphate within the matrix vesicles.
c. Calcium pumps in the membrane of the matrix vesicles bring more calcium into the vesicle, forming calcium hydroxyapatite crystals that grow and eventually puncture the matrix vesicle releasing its contents into the matrix where the crystals form **nidi of crystallization** and the released enzymes free phosphate ions that unite with the calcium forming more calcium phosphate.
d. Calcium phosphate then begins to calcify the matrix around the nidi of crystallization.
e. Water is removed from the matrix permitting hydroxyapatite crystals to be deposited into gaps within the collagen fibrils and the nidi of mineralization enlarge, and fuse with neighboring nidi eventually calcifying the entire matrix.

F. Bone remodeling. Bone is constantly being remodeled as necessary for growth and to alter its structural makeup and also to adapt to changing stresses in the environment throughout life.

1. Early in life, bone development outpaces bone resorption as new haversian systems are added and fewer are resorbed. When the epiphyseal plates are closed, ending bone growth, bone development, and resorption are balanced. Remodeling of compact bone is due mostly to general factors (PTH and calcitonin), whereas remodeling of cancellous bone is due mostly to local factors.

G. Repair of a bone fracture. A bone fracture damages the matrix, bone cells, and blood vessels in the region and is accompanied by localized hemorrhage and blood clot formation.

1. **Proliferation of osteoprogenitor cells** occurs in the periosteum and endosteum in the vicinity of the fracture. As a result of this proliferation, cellular tissue surrounds the fracture and penetrates between the ends of the damaged bone.

2. **Formation of a bony callus** occurs both internally and externally at a fracture site.
   a. The fracture area loses its vascular supply, lowering oxygen tension, and osteoprogenitor cells convert to chondrogenic cells, forming hyaline cartilage and fibrous connective tissue in the fracture zone.
   b. Endochondral bone formation replaces the cartilage with primary bone and intramembranous bone formation also produces primary bone in the area.
   c. The irregularly arranged trabeculae of primary bone join the ends of the fractured bone, forming a **bony callus**. Subsequently, the primary bone is resorbed and replaced with secondary bone as the fracture heals.

CLINICAL CONSIDERATIONS

Bone repair

After severe injury where segments of bone have been lost or must be removed, the remaining bone is prevented from forming a bony union followed by a bony callus that over time would result in completed bone repair. When the bony union is not possible, a bone graft is required. For this purpose, bone fragments that are stored frozen to maintain osteogenic potential may then be utilized in bone grafts.

Autographs are most successful because the bone donor is the recipient. **Homographs** are of bone donated from a different individual. **Heterographs** are the least successful because the donor bone comes from another species. However, calf bone that has been frozen can serve as a viable bone graft when necessary.

H. Role of vitamins in bone formation

1. **Vitamin D** is necessary for **absorption of calcium** from the small intestine. Vitamin D deficiency results in poorly calcified (soft) bone, a condition known as **rickets** in children and **osteomalacia** in adults. Vitamin D is also necessary for **bone formation** (ossification), whereas excess levels of vitamin D cause bone resorption.
2. **Vitamin A** deficiency inhibits proper bone formation and growth, whereas an excess accelerates ossification of the epiphyseal plates. Deficiency as well as excess of vitamin A results in small stature.
3. **Vitamin C** is necessary for **collagen formation**. Deficiency results in **scurvy**, characterized by poor bone growth and inadequate fracture repair.

CLINICAL CONSIDERATIONS

Rickets occurs in children deficient in vitamin D, which results in calcium deficiency. It is characterized by deficient calcification in newly formed bone and is generally accompanied by deformation of the bone spicules in epiphyseal plates; as a result, bones grow more slowly than normal and are deformed by the stress of weight bearing. Rickets is very common in children living in very poor countries where famine and starvation are of frequent occurrence. These children present with bowed legs, are "pigeon chested," and their heads have a square shape. The principal reason for rickets in these countries is a diet consisting mostly of cereals, which are poor in calcium resulting in calcium deficiency with subsequent formation of poorly calcified bone.

Osteomalacia (rickets of adults) results from calcium deficiency. It is characterized by deficient calcification in newly formed bone and decalcification of already calcified bone. This disease may be severe during pregnancy because the calcium requirements of the fetus may lead to calcium loss from the mother.

I. Review of the role of hormones in bone formation

1. **PTH** activates osteoblasts to secrete **RANKL** and **OSF**. The former induces osteoclast formation and the latter activates osteoclasts to **resorb bone**, thus **elevating blood calcium levels**. Excess PTH (hyperparathyroidism) renders bone **more susceptible to fracture** and subsequent deposition of calcium in arterial walls and certain organs, such as the kidney.

2. **Calcitonin** is produced by parafollicular cells (C cells) of the thyroid gland. It eliminates the ruffled border of osteoclasts, induces them to go into apoptosis, and **prevents bone resorption**.
3. **Pituitary growth hormone** (**somatotropin**) is produced in the pars distalis of the pituitary gland. It stimulates overall growth, especially that of epiphyseal plates, and influences bone development via insulin-like growth factors (somatomedins), especially stimulating growth of the epiphyseal plates. Children deficient in this hormone exhibit dwarfism, whereas adults with an excess of somatotropin in their growing years display **pituitary gigantism** and **acromegaly**.

CLINICAL CONSIDERATIONS

Osteoporosis is a disease characterized by **low bone mass** (**low bone mineral density**) and structural deterioration of bone tissue, making the bone fragile and susceptible to fracture. Osteoporosis is associated with an abnormal ratio of mineral to matrix. It results from increased bone resorption, decreased bone formation, or both.

Estrogen activates bone formation by osteoblasts, and, in its absence, an imbalance causes osteoclastic activity to render bones fragile and susceptible to fracture. Osteoporosis is most common in postmenopausal women because of diminished estrogen secretion and in immobile patients because of lack of physical stress on the bone.

Estrogen therapy was employed for decades to minimize the onset of osteoporosis. Recently, it was determined that estrogen replacement therapy increases the risk of heart disease, stroke, breast cancer, and blood clots. Now, instead of estrogen, a recent new group of drugs, the bisphosphonates, has been developed that reduces the incidence of osteoporosis. Preventive measures include a balanced diet rich in calcium and vitamin D and weight-bearing exercise.

Acromegaly results from an **excess of pituitary growth hormone** in adults. It is characterized by **very thick bones** in the extremities and in portions of the facial skeleton.

III. JOINTS

A. Synarthroses **are *immovable joints* composed of connective tissue, cartilage, or bone.** These joints unite the first rib to the sternum and connect the skull bones to each other.

B. Diarthroses (synovial joints) **permit *maximum movement* and generally unite long bones.** These joints are surrounded by a two-layered capsule, enclosing and sealing the articular cavity. The articular cavity contains synovial fluid, a colorless, viscous fluid that is rich in hyaluronic acid and proteins.
   1. The **external** (**fibrous**) **capsular layer** is a tough, fibrous layer of dense connective tissue.
   2. The **internal** (**synovial**) **capsular layer** is also called the **synovial membrane**. It is lined by a layer of squamous to cuboidal epithelial cells on its internal surface. Two cell types are displayed in electron micrographs of this epithelium.
      a. **Type A cells** are intensely phagocytic and have a well-developed Golgi complex, many lysosomes, and sparse RER.
      b. **Type B cells** resemble fibroblasts and have a well-developed RER; these cells probably secrete synovial fluid.

CLINICAL CONSIDERATIONS

Cracking knuckles is a habit that annoys some people who have to listen to individuals who practice the habit. Until recently, no one knew what made the noise and whether the joint producing the noise was unhealthy. MRI studies of the joint while it was being "cracked" demonstrated that small bubbles formed in the synovial fluid of the joint and, when the bubble cavitated, the popping sound was produced. Apparently, joints that can be easily "cracked" were healthier than joints that did not produce the popping sound.

Certain joints, such as the knee joint, have two pieces of fibrocartilage, known as the **menisci** (singular: **meniscus**), interposed between the articulating bones. Because these are weight-bearing structures that are exposed to a great deal of pressure and damaging forces, each meniscus begins

to deteriorate and, eventually, disintegrate. In the United States alone, annually, more than 1 million people have surgery to repair the menisci and almost three-fourths of a million people have to have their knees replaced by artificial knees. The rapid advancements in 3D bioprinting has progressed to such an extent that it is possible to print menisci constructed of a polymer with various cytokines embedded in it as well as stem cells from the individual's own adipose tissue and manufacture the menisci to the exact specifications of the patient's anatomy. Although most of the research has been done on sheep knees, the success and rapid recovery exhibited by these animals has given the impetus to some orthopedic surgeons to perform similar procedures in humans with great success.

A form of inflammatory arthritis caused by accumulation of **uric acid crystals** in joints is known as **gout**, a condition that affects more than 8 million people in the United States alone. If the urate deposit occurs in younger individuals (about 30 years of age) as a function of a metabolic disease, then it is known as **primary gout**; if it occurs in older adults and is due to certain diseases and drug therapy, it is known as **secondary gout**. More males than females are affected up to the time of menopause, after which both genders are affected equally, until 80 years of age when the incidence in females becomes greater than in males. Although almost any synovial joint is susceptible, usually, joints of the big toe, ankle, or the knee are the primary sites of the condition presenting with a red, swollen, painful joint. Primary gout is usually caused by problems with purine metabolism that results in hyperuricemia (caused by elevated production and/or retention of uric acid), whereas secondary gout is the result of diseases such as diabetes mellitus, kidney problems, obesity, elevated blood pressure, alcoholism (especially beer consumption), and lead toxicity as well as of prescription drugs such as diuretics, levodopa, aspirin (low dose for prophylactic use), niacin, and cyclosporine. Additionally, excessive consumption of foods rich in purines, such as sardines, liver, tuna, and shellfish, and drinking fructose-rich juices and soft drinks may increase chances of developing gout. Interestingly, coffee, occasional consumption of white or red wine, and low-fat dairy products appear to reduce the incidence of gout.

Review Test

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A pale, 14-year-old boy, who is tall for his age and has eczema, is seen by his pediatrician because the child broke his humerus as he tripped and fell while walking. The pediatrician asked about the child's diet and daily activities and learned that he spends a lot of time indoors playing on his electronic tablet. The pediatrician assumed that the child has a vitamin deficiency. Which vitamin may be lacking in his diet?

(A) Vitamin B_{12}
(B) Vitamin D
(C) Vitamin E
(D) Vitamin B_6
(E) Vitamin A

2. A 22-year-old woman is seen for the first time by her new physician, who notes that she has very thick bones in her extremities and face. The physician suspects acromegaly, caused by which of the following?

(A) Hypervitaminosis A
(B) Excess growth hormone
(C) Deficiency in growth hormone
(D) Excess calcitonin levels
(E) Deficiency in calcitonin

Questions 3 and 4 are based on the following scenario:

A 25-year-old patient, anemic for several years, complains of failing eyesight and hearing loss. During a physical examination, it is determined that the patient has lost function of some of the cranial nerves.

3. What should the physician suspect as the diagnosis?

(A) Osteoporosis
(B) Osteomalacia
(C) Rickets
(D) Acromegaly
(E) Osteopetrosis

4. What is the cause of the cranial nerve involvements?

(A) Excess calcium levels
(B) Lack of osteoblast activity
(C) Excess osteoblast activity
(D) Lack of osteoclast activity
(E) Excess osteoclast activity

Questions 5 through 7 are based on the following scenario:

A 30-year-old male patient presents with swollen, red, painful joint of his big toe. The patient indicates that he was in bed when the pain suddenly began and is unremitting. The physician orders blood tests and urine tests.

5. What is the suspected diagnosis?

(A) Broken toe
(B) Sprained joint
(C) Osteomyelitis
(D) Primary gout
(E) Tendinitis

6. What abnormality does the physician expect to see in the blood test?

(A) Elevated calcium levels
(B) Elevated uric acid levels
(C) Depressed uric acid levels
(D) Elevated phosphate levels
(E) Depressed phosphate levels

7. The physician counsels his patient to stay away from which of the following?

(A) Red wine
(B) White wine
(C) Beer
(D) Coffee
(E) Skim milk

Questions 8 and 9 refer to the following scenario:

A 4-year-old girl who arrived in the United States a few months ago when her parents emigrated as refugees from Somalia is seen by a pediatrician. He notices that the child's legs are bowed. She is also "pigeon chested," and her skull has a square appearance.

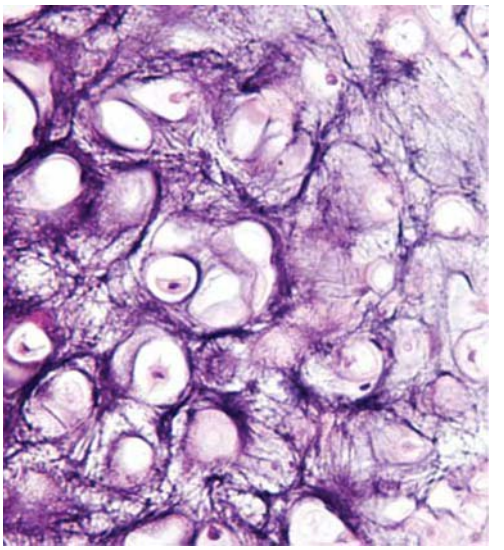
8. What is the pediatrician's suspicion of this child's condition?

(A) Osteopetrosis
(B) Rickets
(C) Osteomalacia
(D) Scoliosis
(E) Osteomyelitis

9. The child is deficient in which of the following substances?

(A) Sodium
(B) Potassium
(C) Vitamin A
(D) Vitamin C
(E) Calcium

Question 10 is based on the following figure:



10. The matrix of the tissue houses which of the following collagen types?

(A) Type I collagen
(B) Type II collagen
(C) Type III collagen
(D) Type IV collagen
(E) Type V collagen

Answers and Explanations

1. **B.** Because vitamin D is necessary for the absorption of calcium, its deficiency leads to calcium loss from the bones. As a result, the bones become fragile.
2. **B.** Excessive growth hormone causes acromegaly but none of the other conditions that are listed.
3. **E.** Osteopetrosis is a genetic defect involving the osteoclasts. Persons with this defect possess osteoclasts without ruffled borders, which prohibit them from resorbing bone.
4. **D.** In osteopetrosis, bone is formed normally but is not resorbed. This leads to increased bone density, anemia, deafness, blindness, and other cranial nerve involvements because the nerves are impinged upon as they exit the cranium via their foramina.
5. **D.** Because the patient is a 30-year-old male and the pain occurred suddenly at night without any evidence of physical trauma, the physician suspects primary gout.
6. **B.** Individuals who have primary gout exhibit elevated uric acid levels because they have abnormal purine metabolism that does not permit normal clearance of uric acid.
7. **C.** Beer is one of the drinks that raises plasma uric acid levels. The other drinks that are listed either have no effect on uric acid levels or actually depress plasma levels of uric acid.
8. **B.** The child is a refugee from Somalia where she was malnourished, resulting in the presence of the principal symptoms of rickets: bowed legs, pigeon chest, and square-shaped head.
9. **E.** Because the main nutrition consisted of cereal, the child's diet was lacking in calcium. The deficiency of calcium resulted in poorly calcified bones that bent under her body weight, making her bow-legged. Her head also took on the characteristic square shape, and her chest became deformed, presenting with the pigeon-chest appearance.
10. **B.** The image is of elastic cartilage, and the type of collagen in its matrix is type II collagen.

chapter 7

Muscle

I. OVERVIEW—MUSCLE

The two types of muscle are **striated** and **smooth**, and striated muscle has two subdivisions: **skeletal** and **cardiac muscles**. All muscle cells, also known as **muscle fibers**, possess **contractile elements** whose major components are the proteins **actin** and **myosin**. Contraction may be **voluntary** (skeletal muscles) or **involuntary** (cardiac and smooth muscles).

II. SKELETAL MUSCLE STRUCTURE

A. Connective tissue investments of skeletal muscles not only convey neural and vascular elements to the muscle cells but also provide a vehicle that harnesses the forces of muscle contraction. An entire skeletal muscle (such as the biceps) is surrounded by a thick connective tissue known as the **epimysium**, which forms **aponeuroses** that connect skeletal muscle to skeletal muscle, and **tendons** that connect skeletal muscle to bone. **Fascicles** (small bundles of muscle cells) are surrounded by a **perimysium**, whereas individual skeletal muscle cells are surrounded by an **endomysium** composed of reticular fibers and an external lamina.

B. Skeletal muscle cell types

1. Types of skeletal muscle cells include **red** (**type I**), distinguished by its slow contraction and its ability not to fatigue easily; **white** (**type IIb**), which contracts rapidly but fatigues easily; and **intermediate** (**type IIa**) with characteristics that resemble both types I and IIb. All three types may be present in a given muscle, and each muscle has its particular, more or less constant, combination of the three types of cells.
2. These three cell types differ from each other in their content of **myoglobin** (a protein that is similar to hemoglobin in that it binds O_2), **number of mitochondria**, **concentration** of various enzymes, and **rate** of contraction (Table 7.1).
3. A change in **innervation** can change a fiber's type. If a red fiber is denervated and its innervation is replaced with that of a white fiber, the red fiber will change its characteristics and will become a white fiber.

C. Skeletal muscle cells (Figs. 7.1 to 7.3) are long, cylindrical, and *multinucleated*; each cell is enveloped by an endomysium. The cytoplasm of muscle cells is also called **sarcoplasm**; the plasmalemma is **sarcolemma**, which, in striated muscle, forms deep tubular invaginations, or **T (transverse) tubules**, which extend deep into the sarcoplasm. Skeletal muscle cells possess cylindrical collections of **myofibrils**, 1 to 2 μm in diameter, which extend the entire length of the cell.

1. **Myofibrils** are composed of longitudinally arranged, cylindrical bundles of **thick** and **thin myofilaments** observable by transmission electron microscopy (Fig. 7.1).

table 7.1 Characteristics of Red and White Muscle Fibers

Type	Myoglobin Content	Number of Mitochondria	Enzyme Content	Contraction	Primary Method of ATP Generation
Red (slow; type I)	High	Many	High in oxidative enzymes; low in ATPase	Slow but repetitive; not easily fatigued	Slow oxidative phosphorylation
Intermediate (type IIa)	Intermediate	Intermediate	Intermediate in oxidative enzymes and ATPase	Fast but not easily fatigued	Oxidative phosphorylation and anaerobic glycolysis
White (fast; type IIb)	Low	Few	Low in oxidative enzymes; high in ATPase and phosphorylases	Fast and easily fatigued	Anaerobic glycolysis

ATP, adenosine triphosphate; ATPase, adenosine triphosphatase.

2. The **sarcomere** is the region between two adjacent Z disks in a myofibril and constitutes the **functional unit of contraction** in skeletal muscle.
3. The **sarcoplasmic reticulum** (**SR**) is a modified smooth endoplasmic reticulum that surrounds myofilaments and forms a meshwork around each myofibril. It forms a pair of dilated **terminal cisternae**, which encircle the myofibrils at the junction of each A and I band and **regulates muscle contraction** by sequestering calcium ions (leading to relaxation) or releasing calcium ions (leading to contraction).
4. **Triads** are specialized complexes consisting of a narrow central T tubule flanked on each side by terminal cisternae of the SR (Fig. 7.1). They are located at the A–I junction in mammalian skeletal muscle cells and **help provide uniform contraction** throughout the muscle cell.
5. **Myofilaments** include **thick filaments** (15 nm in diameter and 1.5 µm long) and **thin filaments** (7 nm in diameter and 1.0 µm long). They lie parallel to the long axis of the myofibril in a precise arrangement that is responsible for the sarcomere banding pattern.

CLINICAL CONSIDERATIONS

One of the most aggressive neoplasms involving skeletal muscles is **rhabdomyosarcoma**, of which the most commonly occurring in the young adolescent is **alveolar rhabdomyosarcoma**. This neoplasm, usually restricted to the deep muscles of the arms and legs, is subdivided into clusters by fibrous connective tissue septa, and, when the cells in the center of each cluster die, the empty spaces give the impression of alveoli of the lung. In about a quarter of the cases, cells exhibit cross-striations. Possibly, this condition arises as a function of chromosomal translocations. Treatment usually requires surgical excision followed by chemotherapy and sometimes radiation. The prognosis is much better in children, 65% of whom survive if the treatment is initiated during the early phases of the disease.

D. **Satellite cells** (***myoblast-like cells, regenerative cells***) **are probably residual cells from embryonic development that lie within the external lamina (basal lamina) of skeletal muscle cells and adhere to these cells via *M-cadherin molecules***. To be able to form new skeletal muscle cells, satellite cells have to become activated by damage to the muscle or possibly by mechanical stresses placed on the skeletal muscle. The activated satellite cells, under the influence of **myogenic regulatory factors** such as **Myo-D**, become myoblasts that fuse with each other to form myotubes and differentiate into mature skeletal muscle cells.

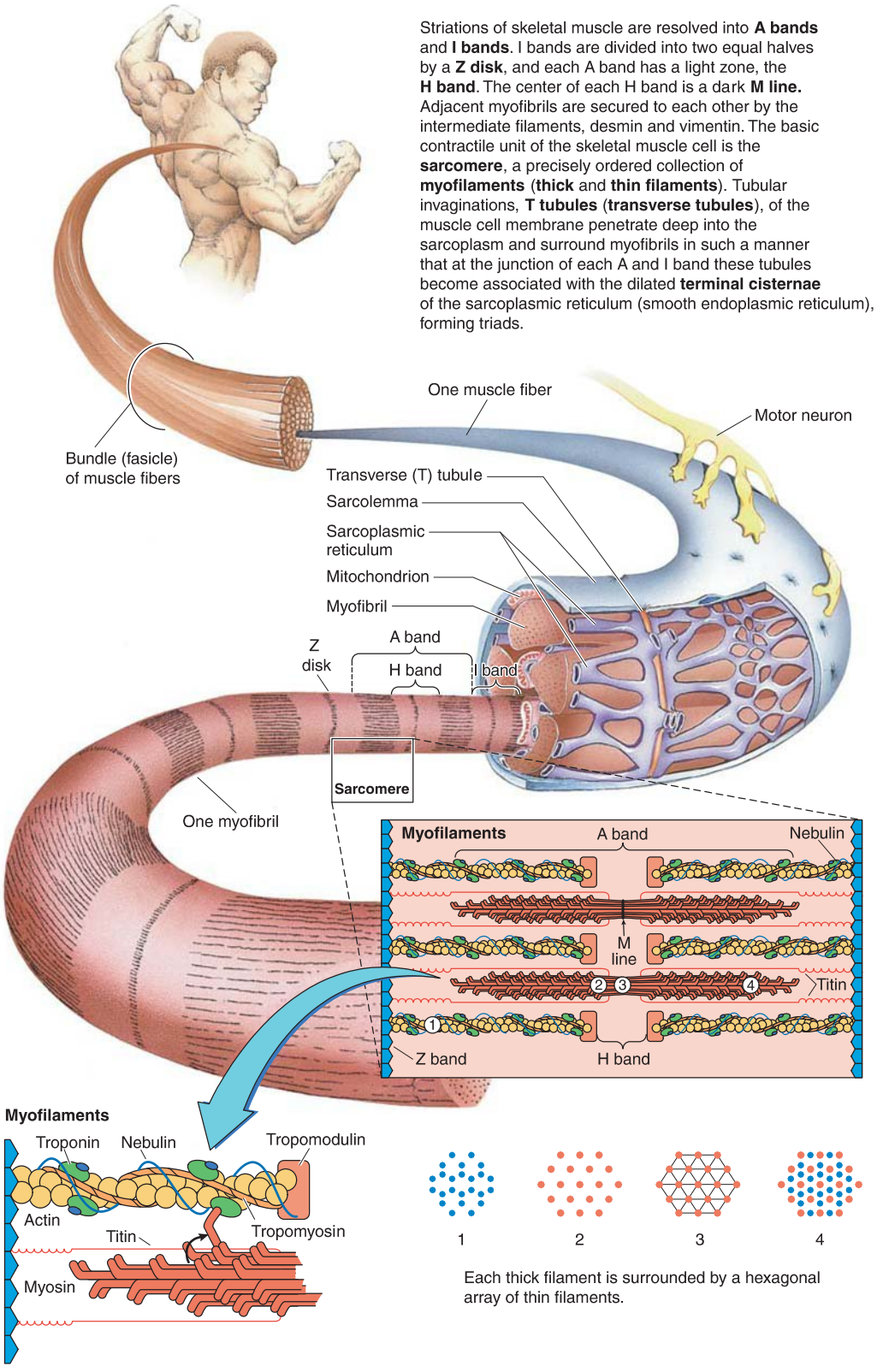


FIGURE 7.1. Diagram of skeletal muscle and its components as observed by light and electron microscopy. (Reprinted with permission from Gartner LP. *Atlas of Histology*. 7th ed. Baltimore, MD: Wolters Kluwer; 2018:150.)

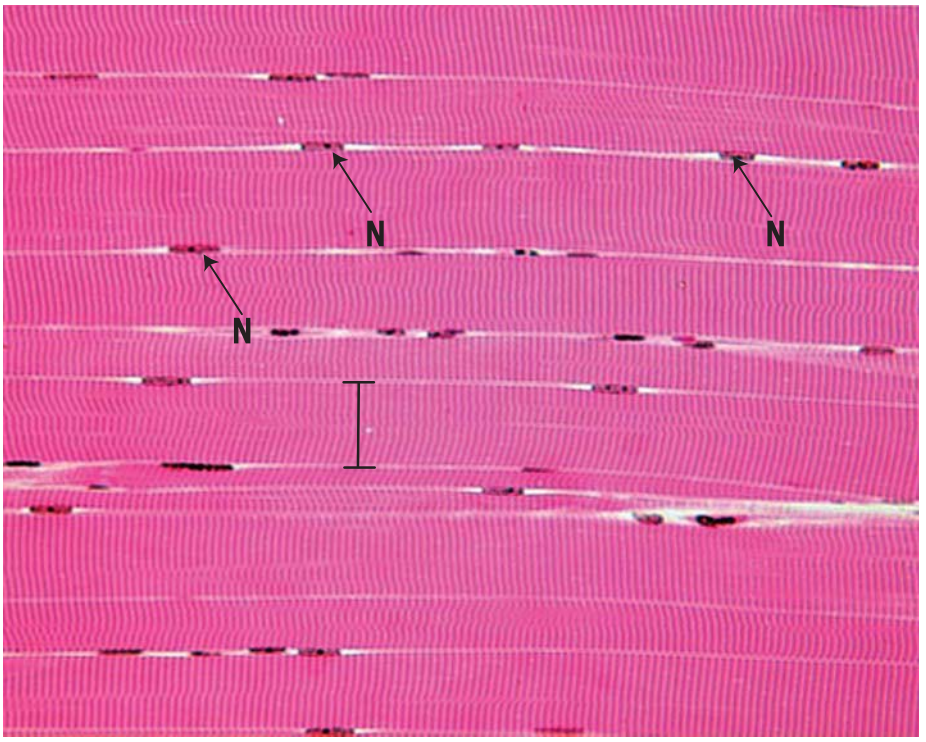


FIGURE 7.2. Light micrograph of a longitudinal section of monkey skeletal muscle (×270). Note that the bar in the middle delineates the width of a single skeletal muscle fiber. N, nuclei.

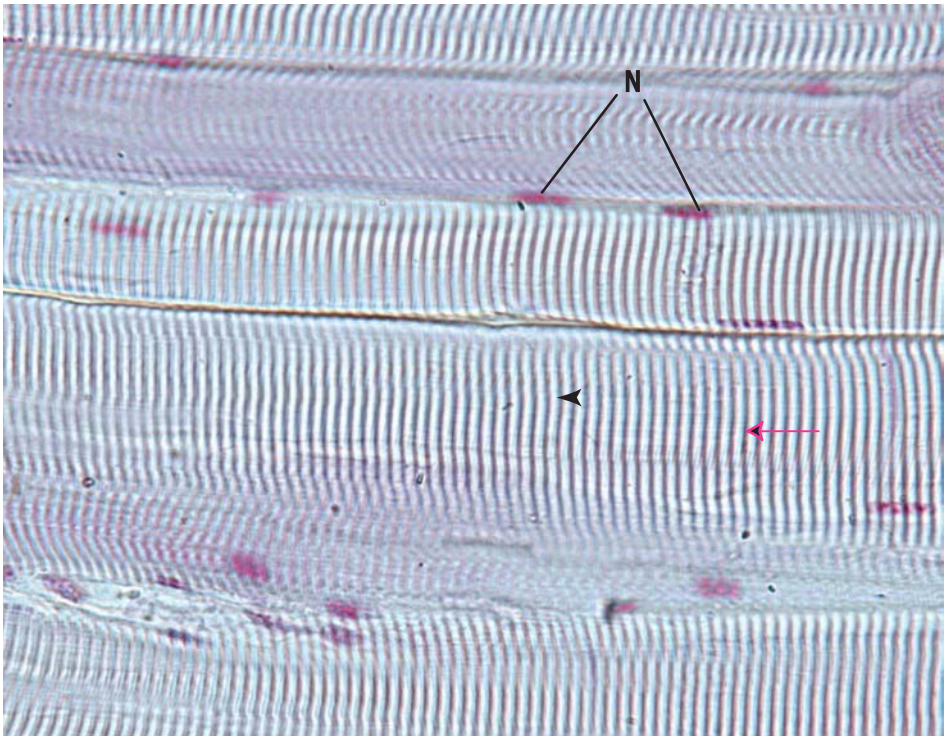


FIGURE 7.3. This is a higher magnification of a region similar to that of Figure 7.2. Note that the nuclei (N) of the skeletal muscle cells are located at the periphery of the fibers (×540). *Arrowhead*, I band; *red arrow*, A band.

CLINICAL CONSIDERATIONS

In order to ensure that a muscle cell does not become overly long or broad, muscle cells manufacture and release a protein, **myostatin**, a member of the tumor growth factor-β superfamily, that restricts the size of individual skeletal muscle cells.

Anabolic steroid use is prevalent among athletes and high school–aged male students. An estimated almost 10% of high school–aged male students use anabolic steroids (similar to testosterone) to increase their muscle mass. Approximately 65% of the abusers of anabolic steroids are football and baseball players, weight lifters, and wrestlers. Of the two forms, tablets and injections, the tablets are more insidious because they may cause jaundice and liver damage as well as aspermia, reduction in testis size, and breast induction in males. In females, anabolic steroid use may result in a decrease in breast size, irregular menstrual cycles, and male-pattern baldness. Additional side effects are increased libido, increased acne, mood swings, and aggressive behavior that may develop into physical violence. The presence of anabolic steroids is detectable in the body fluids for 6 months after the last dose was taken.

E. Skeletal muscle cross-striations (Fig. 7.1)

1. **A bands** are anisotropic with polarized light; they usually stain dark. They contain **both thin** and **thick filaments**, which overlap and interdigitate. Six thin filaments surround each thick filament (Fig. 7.1).
2. **I bands** are isotropic with polarized light and appear lightly stained in routine histologic preparations. They contain only **thin filaments**.
3. **H bands** are light regions transecting A bands; they consist of **thick filaments** only.
4. **M lines** are narrow, dark regions at the center of H bands formed by several cross-connections (**M-bridges**) at the centers of adjacent thick filaments.
5. **Z disks** (**lines**) are dense regions bisecting each I band.
   a. Z disks contain **α-actinin** and **Cap Z**, two proteins that bind to thin filaments and anchor them to Z disks with the assistance of **nebulin**.
   b. **Desmin** (and during embryonic development also **vimentin**), aided by **plectin**, anchors Z disks to one another. Peripherally located Z disks are anchored to regions of the sarcolemma, known as **costameres**, **dystrophin-associated glycoprotein complexes**.

CLINICAL CONSIDERATIONS

Desmin-related myopathy (**DRM**) is a rare, inherited disease in which a mutation is responsible for the formation of desmin molecules that form desmin aggregates rather than the normal desmin filaments. The absence of filamentous desmin results in disorganized myofilaments and skeletal muscle fibers. The symptoms of the disease begin as progressive weakness in the muscles of the legs, followed by weakness in the trunk and the rest of the body. Because DRM also affects cardiac and smooth muscles, respiratory insufficiency, heart failure, and impaired gastrointestinal functions follow with possibly fatal consequences.

Ethanol myopathy may occur as a result of binge drinking. This condition is characterized by destruction of skeletal muscle fibers (rhabdomyolysis) associated with myoglobinuria (myoglobin in the urine). In more severe cases, the patient frequently complains about weakness and pain of the affected muscles (or sometimes all muscles) as well as nausea; vomiting; and, occasionally, confusion and even the possibility of renal failure. The urine may also be darker than normal because of the released myoglobin. Muscle biopsies present with swollen, degenerating muscle cells and phagocytosis of damaged muscle fibers. Regeneration attempts by the muscle may also be evident.

Drug-induced myopathies may occur as a result of **steroid use**, either for medical or for athletic reasons. Usually only white and intermediate muscle fibers (type IIa and type IIb cells) atrophy, but, in severe cases, red fibers (type I) may also be involved. The use of chloroquine (drug formerly used in malaria treatment but now used in treating other conditions) may also result in drug-induced myopathies in type IIa and IIb skeletal muscle cells.

(1) **Costameres** are specialized areas of the sarcolemma located at regions that correspond to the Z-lines of myofibrils that are situated just beneath the striated muscle cell membrane. Costameres are defined by the presence of peripheral and transmembrane protein complexes whose principal moieties are localized on the sarcoplasmic aspect of the striated muscle cell membrane.

(2) **Dystrophin-associated glycoprotein complexes** are composed of several protein groups, including dystrophin, sarcoglycan complex, dystroglycan complex, syntrophins, and dystrobrevin.

- (a) **Dystrophin** is a pencil-shaped molecule that is the lynchpin between the extracellular matrix (ECM) and the cytoskeleton attached to the peripheral most myofibril of the striated muscle fiber. It plays the greatest role in strengthening and maintaining the integrity of the sarcolemma during the process of contraction.
- (b) **Sarcoglycan complex** is composed of several transmembrane proteins localized at the costameres of the sarcolemma, which form attachments to and reinforce the dystroglycan complex.
- (c) **Dystroglycan complex** is a complex of two transmembrane proteins whose extracellular domains bind to **laminin** of the external lamina of the muscle cells. Intracellularly dystroglycan binds to dystrophin as well as to **syntrophins**.
- (d) **Syntrophins** are relatively small proteins, approximately 60 kDa, that form bonds not only with dystrophins but also with desmin and dystrobrevin.
- (e) The protein **dystrobrevin** has binding sites with syntrophins and with desmin. Therefore, the dystrophin-associated glycoprotein complex forms a series of bonds *centered around* dystrophin. These function to affix the desmin intermediate filaments to ECM laminin, providing them with the ability to maintain the precise orientation and arrangement of the Z-lines of adjacent myofibrils throughout the entire skeletal muscle cell. These attachments to the glycoprotein laminin of the ECM occur in the costamere regions of the sarcolemma.

CLINICAL CONSIDERATIONS

Muscular dystrophies differ from **myopathies**: **Dystrophies** are a varied constellation of familial conditions that may become evident in preteens or early teens as weakness in muscle groups that progresses with time to a wasting condition. Biopsies of the muscle groups display the presence of fibrous and fatty connective tissue in place of skeletal muscle cells.

Myopathies are also characterized by muscle weakness and wasting that may or may not be inherited; they are commonly associated with metabolic disease and aberrant mitochondrial function and, occasionally, are due to infections, inflammations, and the presence of toxins. However, biopsies of the muscle groups do not display the presence of fibrous and fatty connective tissue in place of skeletal muscle cells, although lipid droplets may be present within the affected skeletal muscle cells.

Duchenne muscular dystrophy (**DMD**) is caused by a **sex-linked**, recessive genetic defect that results in the inability to synthesize **dystrophin**, an actin-binding protein normally present in small amounts in the sarcoplasm. Dystrophin also stabilizes the sarcolemma and acts as a link between the cytoskeleton and the ECM. This common, serious degenerative disorder occurs in young men and results in death usually before 20 years of age. It is characterized by the replacement of degenerating skeletal muscle cells by fatty and fibrous connective tissue, but it may also affect cardiac muscle.

Facioscapulohumeral muscular dystrophy (**FSHMD**, or **Landouzy–Dejerine syndrome**) is not sex linked, but is an **autosomal dominant** genetic defect that results in "wasting" of the skeletal muscles of the face, those around the scapula, and those of the upper arm, initially. As the disease progresses, it affects skeletal muscles of other areas of the body. It is one of the most common forms of muscular dystrophy and manifests itself in the late teens and early 20s. Many affected patients suffer hearing loss, abnormal heart rhythm, and dilations of the blood vessels in the retina of the eye (retinal telangiectasia). The disease does not impinge on life expectancy, and 85% of affected individuals do not become wheelchair bound.

F. Myofilament molecular organization

1. **Thin filaments** are composed of F-actin, tropomyosin, troponin, and associated proteins.
   a. **F-actin** (Fig. 7.1) is a polymer of G-actin monomers arranged in a double helix, where each monomer possesses an **active site** that can interact with myosin. It is present as filaments (with a diameter of 5–7 nm) that exhibit **polarity**, having a plus (+) and a minus (−) end. The plus end is tethered to Cap Z of the Z disk. The minus end, the growing end of the F-actin, is located at the H band and is capped by **tropomodulin**, preventing the addition of more G-actin to the end of the thin filament.
   b. **Tropomyosin** molecules are about 40 nm in length. They bind head to tail, forming filaments that are located in the grooves of the F-actin helix.
   c. **Troponin**, associated with each tropomyosin molecule, is composed of the following:
      (1) **Troponin T** (**TnT**) forms the tail of the molecule; it functions in binding the troponin complex to tropomyosin.
      (2) **Troponin C** (**TnC**) possesses four binding sites for calcium. It may be related to calmodulin.
      (3) **Troponin I** (**TnI**) binds to actin and inhibits interaction of myosin and actin.
   d. **Nebulin** is a long, inelastic protein. Two nebulin molecules wrap around each thin filament and assist in anchoring it to the Z disk (Fig. 7.1).
      (1) Each nebulin molecule is embedded in the Z disk by its carboxyl terminal and its amino terminal ends at the A band at or near the free end of its thin filament.
      (2) Nebulin in skeletal muscle is thought to determine the length of its associated thin filament; in cardiac muscle, it extends only one quarter of the length of the thin filament.
2. Each **thick filament** is composed of approximately 250 **myosin II** molecules (arranged in an antiparallel fashion) and the associated proteins—myomesin, titin, and C protein—as well as the enzyme creatine kinase.
   a. **Myosin II** (Fig. 7.1) is composed of two identical heavy chains and two pairs of light chains. At least 18 different subtypes of myosin exist, and the one present in skeletal muscle is myosin II. This particular type of myosin molecule resembles a double-headed golf club and from this point on it will be referred to as just "myosin."
      (1) Myosin **heavy chains** consist of a long rodlike "tail" and a globular "head." The tails of the heavy chains wind around each other in an α-helical configuration. Tails function in the self-assembly of myosin molecules into bipolar thick filaments, whereas the actin-binding sites of the heads function in contraction.
      (2) Myosin **light chains** are of two types; one molecule of each type is associated with the globular head of each heavy chain.
      (3) **Enzymatic digestion of myosin**
         (a) **Trypsin** cleaves myosin into **light meromyosin** (part of the tail portion) and **heavy meromyosin** (the two heads and the remainder of the tail) (Fig. 7.1).
         (b) The enzyme **papain** cleaves the heavy meromyosin, releasing the short tail (**S2 fragment**) and the two globular heads (**S1 fragments**). The S1 fragments have adenosine triphosphatase (ATPase) activity but require interaction with actin to release the noncovalently bound adenosine diphosphate (ADP) and P_i.
   b. **Myomesin** and **creatine kinase** are located at the M line. The former affixes adjacent thick filaments to one another to maintain their precise spatial relations; the latter is an enzyme that removes a phosphate group from creatine phosphate to phosphorylate ADP, converting it to the energy-rich compound ATP.
   c. **C protein**, which occupies the **C zone**, binds to thick filaments between the M line and the end of the thin filament in the vicinity of the A–I junction.
   d. **Titin** is a large linear protein that displays axial periodicity. It forms an elastic lattice that parallels the thick and thin filaments. Two titin proteins anchor each thick filament to the Z disk, thus maintaining the architectural relationships of the thick filaments to each other (Fig. 7.1).
      (1) The **amino terminal** of the titin molecule spans the entire thickness of the Z disk and binds to α-actinin and Z proteins. Within the Z disk, titin overlaps with other titin molecules from the neighboring sarcomere and probably forms bonds with them or with unidentified linker proteins.
      (2) The **carboxyl terminal** of the titin molecule spans the entire M line, overlapping with titin molecules from the other half of the same sarcomere, and binds to the protein **myomesin**.
      (3) Within the I band, in the vicinity of the Z disk, titin interacts with thin filaments and within the A band, titin interacts with **C protein**.

III. SKELETAL MUSCLE CONTRACTION

The contraction cycle (Fig. 7.4) involves the binding, hydrolysis, and release of adenosine triphosphate (ATP).

A. Huxley's sliding-filament model (Table 7.2)

1. During contraction, thin filaments slide past thick filaments and penetrate deeper into the A band, which remains constant in length; however, the I bands and H bands shorten as Z disks are drawn closer together.
2. Neither the thick filament nor the thin filaments become shortened; instead, they increase their overlap.

B. Initiation and regulation of contraction

1. Depolarization, accompanied by the release of Ca^{2+}, triggers the binding of actin and myosin, leading to muscle contraction.

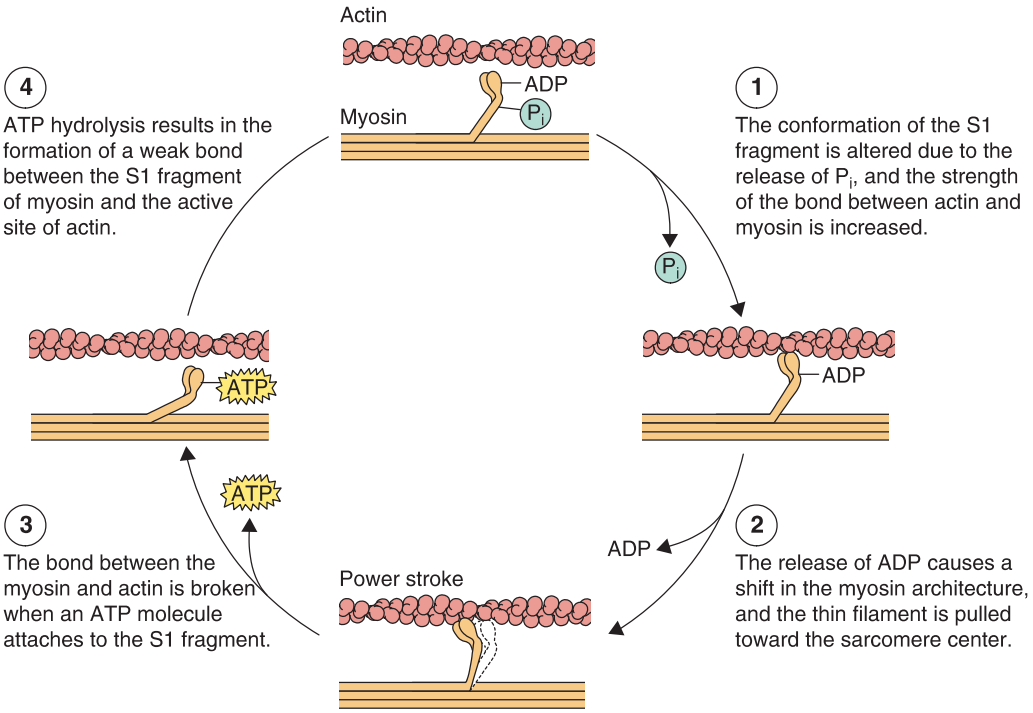


FIGURE 7.4. Contraction cycle in skeletal muscle cells. This sequence of steps is repeated many times, leading to extensive overlay of thick and thin filaments, which shortens the sarcomere and consequently the entire skeletal muscle fiber. ADP, adenosine diphosphate; ATP, adenosine triphosphate; P_i, phosphate group. (Copyright from Alberts B, Bray D, Lewis J, et al. *Molecular Biology of the Cell.* 3rd ed. New York, NY: Garland Science; 1994. Adapted with permission from Garland Science/Taylor & Francis LLC.)

table 7.2 Effects of Contraction on Skeletal Muscle Cross-Bands

Bands	Myofilament Component	Change in Bands Daring Contraction
I	Thin only	Shorten
H	Thick only	Shorten
A	Thick and thin	No change in length
Z disks	Thin only (attached by α-actinin)	Move closer together

a. The **sarcolemma** is depolarized at the myoneural junction, and the wave of depolarization is conveyed to the myofibrils by the **T tubules**. The conformation of **voltage-sensitive dihydropyridine** (**DHP**) **receptors** becomes altered because of membrane depolarization.
b. **Ca^{2+}** is released into the cytosol at the A–I junctions via **Ca^{2+}-release channels** (**junctional feet, ryanodine receptors**) of the SR terminal cisternae that are opened by activated DHP receptors. As long as the Ca^{2+} level is sufficiently high, the contraction cycle will continue.

2. **Activation of actin by Ca^{2+}**
   a. In the **resting state**, the myosin-binding sites on thin (actin) filaments are partially covered by tropomyosin. Also, TnI is bound to actin and hinders myosin–actin interaction.
   b. Ca^{2+} binding by TnC results in a **conformational change** that breaks the TnI–actin bond; tropomyosin shifts its position slightly and uncovers the myosin-binding sites (**active state**).
3. **Contraction cycle** (Fig. 7.4)
   a. The **S1 fragment of myosin II** releases a phosphate group (P_i), but the ADP remains attached to the S1 fragment; the release of the P_i causes a conformational change leading to a strong bond between the actin filament and the S1 fragment.
   b. The ADP molecule is released from the S1 fragment of myosin II, which results in an alteration of the myosin II molecule, and the thin filament is pulled toward the middle of the sarcomere for a distance of 5 nm; this is known as the **power stroke**.
   c. An ATP molecule becomes attached to the S1 fragment, resulting in the release of the S1 fragment from the thin filament.
   d. The ATP is hydrolyzed and a weak bond is formed between the actin filament and the S1 fragment of myosin II. If the contraction continues, then the cycle continues as the S1 fragment of myosin II releases a phosphate group (P_i), but the ADP remains attached to the S1 fragment; the release of the P_i causes a conformational change, leading to a strong bond between the actin filament and the S1 fragment.
   e. For a complete contraction in which a sarcomere is shortened by approximately 1 μm, the cycle just described for a single myosin II molecule must be repeated approximately 200 times.

CLINICAL CONSIDERATIONS

Muscle contraction requires the **expenditure of energy** and skeletal muscle cells derive their energy from glucose. Extended exercise begins to exhaust the blood's glucose supply, reducing the amount of glucose available for the brain. This diminished availability results in the brain shutting down the physical activity, a process that beginning athletes refer to as "hitting the wall." As athletes continue to train, they become more proficient and build up their stamina because their muscles readjust their energy source from glucose to lipids, thereby ensuring a steady supply of glucose to be used by the brain and other organs of the body.

C. **Relaxation depends on a *Ca^{2+} pump* in the SR, which pumps Ca^{2+} from the cytosol to the inner surface of the SR membrane to be bound by *calsequestrin*.** When Ca^{2+} concentration in the cytosol is reduced enough that TnC loses its bound Ca^{2+}, relaxation occurs. As a result, tropomyosin returns to its resting position, covering actin's binding sites and restoring the resting state.

CLINICAL CONSIDERATIONS

Rigor mortis is a postmortem rigidity appearing as hardening of skeletal muscles caused by the inability of muscle cells to synthesize ATP. As a result, myosin remains bound to actin, and the muscles remain contracted because ADP remains attached to the S1 fragment; the release of the P_i causes a conformational change leading to a strong bond between the actin filament and the S1 fragment. In human adults, under ambient temperature conditions, rigor mortis begins about 4 hours after death, reaching its greatest rigidity about 12 to 14 hours after the person died. Within 60 to 75 hours after death, the myofilaments begin to decompose and the rigidity of the muscles begins to weaken. Different muscles begin their rigidity at different times after death; muscles of the face and neck reach rigidity earlier (2–4 hours after death) than those of the extremities (4–6 hours after death). Forensic pathologies use various time tables that take into account the position of the body and the temperature to which the body was exposed. They also utilize the change in the rectal temperature of the body (**algor mortis**) in comparison to the normal body temperature and use the difference multiplied by a constant to determine the number of hours that the person has been dead.

D. **A motor unit consists of a neuron and every muscle cell it innervates.** A **muscle** may contract with varying degrees of strength because only some of the muscle cells contract, but an individual muscle cell obeys the "**all or none law**" (i.e., it either contracts or does not contract). All muscle cells of a single motor unit contract in unison; a large muscle such as the trapezius may have thousands of muscle cells in a motor unit, whereas a muscle such as the superior oblique muscle of the eye may have as few as 10 to 15 muscle cells in a motor unit.

CLINICAL CONSIDERATIONS

Normally, as a muscle contracts the sarcomeres shorten and, consequently, the entire muscle becomes shorter, this type of contraction is referred to as *concentric contraction*, as in picking up a dumbbell and doing curls. Another type of contraction is *isometric contraction*, where the sarcomeres do not shorten; thus, the entire muscle remains the same length, as in squeezing a hard object such as a solid metal ball.

IV. SKELETAL MUSCLE INNERVATION

Innervation consists of **motor** nerve endings (myoneural junctions) and two types of **sensory** nerve endings (muscle spindles and Golgi tendon organs [GTOs]). Both types of sensory nerve endings function in **proprioception**.

A. **The myoneural junction (neuromuscular junction) is a *synapse* between a branch of a motor nerve axon and a skeletal muscle cell.**

1. **Structural components**
   a. The **axon terminal** contains mitochondria, **synaptic vesicles** (containing the neurotransmitter **acetylcholine** [**ACh**]), and smooth endoplasmic reticulum (SER) elements. It has a **Schwann cell**, but *lacks* myelin, on its *nonsynaptic surface*. The membrane on the *synaptic surface* of the axon terminal is called the **presynaptic membrane**.
   b. The **synaptic cleft** is a narrow space between the presynaptic membrane of the axon terminal and the **postsynaptic membrane** (also known as the **motor endplate**) of the muscle cell. The synaptic cleft contains an amorphous **external lamina**, a basal lamina–like material, derived from the muscle cell.
   c. **Muscle cell near the myoneural junction**
      (1) Sarcolemmal invaginations (of the postsynaptic membrane), called **junctional folds**, are lined by an external lamina and extend inward from the synaptic cleft. **ACh receptors** are located in the postsynaptic membrane at the peaks of the junctional folds.
      (2) The sarcoplasm is rich in mitochondria, ribosomes, and rough endoplasmic reticulum (RER).

2. **Conduction of a nerve impulse across a myoneural junction**
   a. When the presynaptic membrane is depolarized **voltage-gated Ca^{2+} channels** open, permitting the entry of extracellular Ca^{2+} into the axon terminal, which triggers the synaptic vesicles to release ACh in multimolecular quantities (**quanta**) into the synaptic cleft. A quantum is approximately equivalent to 20,000 ACh molecules.
   b. The released ACh binds to ACh receptors (**transmitter-gated Na^+ ion channels**) located on the peaks of the junctional folds, resulting in a conformational change of the gate, permitting the influx of Na^+ ions, with a consequential **depolarization** of the sarcolemma and generation of an **action potential**.
   c. The enzyme **acetylcholinesterase**, located in the external lamina lining the junctional folds of the motor endplate, degrades ACh, thus ending the depolarizing signal to the muscle cell.
   d. ACh is recycled as **choline** and returned to the axon terminal to be recombined with acetyl coenzyme A (CoA) (from mitochondria), catalyzed by the enzyme **choline acetyl transferase**, to form ACh, which is then stored in synaptic vesicles.
   e. Membranes of the emptied synaptic vesicles are recycled via **clathrin-coated endocytic vesicles** (see the Section VII in Chapter 1).

CLINICAL CONSIDERATIONS

Amyotrophic lateral sclerosis (**ALS**, or **Lou Gehrig's disease**) is marked by degeneration of motor neurons of the spinal cord as well as upper motor neurons of the brain, resulting in muscle atrophy. A small percent of the affected individuals are affected through autosomal dominant inheritance that appears to point, in some cases, to the superoxide dismutase gene located on chromosome 21. Other mutations have also been discovered that may involve GTPase regulatory systems, and still others may point to glutamate toxicity. Histologic studies of the spinal cord display a decrease in the population of ventral horn motoneurons, and similar studies of the brain show a similar decrease in the number of motoneurons in the motor nuclei of the trigeminal (CN V), nucleus ambiguus (whose fibers join CN IX, X, and XI), and hypoglossal (CN XII) nerves. The symptoms develop over time as more and more neurons succumb to the condition. Early on, the individual notices dropping objects, loss of manual dexterity, and jerky hand and arm movements. As the disease advances, the motor movements become more spastic; muscle weakness becomes more pronounced; and, as respiration becomes problematic, pulmonary infections become recurrent. Eventually, the condition deteriorates to such an extent that the muscles of respiration fail and the patient succumbs to the disease.

Myasthenia gravis is an **autoimmune disease** in which **antibodies block ACh receptors** of myoneural junctions, reducing the number of sites available for initiation of sarcolemma depolarization. It occurs mostly in men over 60 years of age and in women over 40 years of age, but rarely in children.

It is characterized by gradual weakening of skeletal muscles, especially the most active ones (e.g., muscles of the eyes, tongue, face, and extremities). Death may result from respiratory compromise and pulmonary infections. Clinical signs include thymic hyperplasia (thymoma) and the presence of circulating antibodies to ACh receptors.

Botulism is a form of **food poisoning** caused by ingestion of Clostridium botulinum toxin, which inhibits ACh release at myoneural junctions. Botulism is marked by muscle paralysis, vomiting, nausea, and visual disorders and is fatal if untreated.

B. The muscle spindle (neuromuscular spindle) **is an elongated, fusiform sensory organ within skeletal muscle that functions primarily as a *stretch receptor*.** It is bounded by a connective tissue capsule enclosing the fluid-filled **periaxial space** and 8 to 10 modified skeletal muscle fibers **(intrafusal fibers)**. Normal skeletal muscle cells **(extrafusal fibers)** surround it. The capsule of the muscle spindle anchors it to the perimysium and endomysium of the extrafusal fibers.

1. **Function**
   a. **Stretching of a muscle** also stretches the muscle spindle and thus stimulates the afferent nerve endings to send impulses to the central nervous system. The response is to both the **rate** (**phasic response**) and **duration** (**tonic response**) of stretching.
   b. **Depolarization of γ-efferent neurons** also stimulates the intrafusal nerve endings; the rate and duration of the stimulation are monitored in the same way as stretching.
   c. **Muscle overstimulation** results from stretching at too great a frequency or for too long a time period. Overstimulation causes firing of the **α-efferent neurons**, initiating muscle contraction thus counteracting the stretching.

C. The GTOs, **composed of encapsulated *collagen fibers* that are surrounded by terminal branches of *type Ib sensory nerves*, are located in tendons, where they counteract the effects of muscle spindles.** The GTO is stimulated when the muscle contracts too strenuously, increasing tension on the tendon. Impulses from type Ib neurons **inhibit** α-efferent (motor) neurons to the muscle, preventing further contraction.

V. CARDIAC MUSCLE

A. General features—cardiac muscle cells **(Table 7.3)**

1. Cardiac muscle cells **contract spontaneously** and **display a rhythmic beat**, which is modified by hormonal and neural (sympathetic and parasympathetic) stimuli.

table 7.3 Comparison of Skeletal, Cardiac, and Smooth Muscle

Property	Skeletal Muscle	Cardiac Muscle	Smooth Muscle
Shape and size of cells	Long, cylindrical	Blunt-ended, branched	Short, spindle shaped
Number and location of nucleus	Many, peripheral	One or two, central	One, central
Striations	Yes	Yes	No
T tubules and sarcoplasmic reticulum	Has triads at A–I junctions	Has dyads at Z disks	Has caveolae (but no T tubules) and some smooth endoplasmic reticulum
Gap junctions	No	Yes (in intercalated disks)	Yes (in sarcolemma); known as the nexus
Sarcomere	Yes	Yes	No
Regeneration	Restricted	Limited	Extensive
Voluntary contraction	Yes	No	No
Distinctive characteristics	Peripheral nuclei	Intercalated disks	Lack of striations

2. They have one centrally located nucleus (or occasionally two nuclei) and contain **glycogen granules**, especially at either pole of the nucleus; the sarcoplasm is rich in **myoglobin**; and the cells may branch at their ends to form connections with adjacent cells.
3. They possess thick and thin filaments arranged in **poorly defined myofibrils** and exhibit a cross-banding pattern identical to that in skeletal muscle.
4. Cardiac muscle cells have a limited ability to **regenerate**; most injuries to cardiac muscle are repaired by the formation of fibrous connective tissue (scar tissue) by fibroblasts.

B. Structural components of cardiac muscle cells differ from those of skeletal muscle as follows:

1. **T tubules** are larger than those in skeletal muscle and are lined by external lamina. They invaginate from the sarcolemma at Z disks, not at A–I junctions as in skeletal muscle.
2. The **SR** is poorly defined and contributes to the formation of **dyads**, each of which consists of one T tubule and one profile of SR. SR is also present in the vicinity of Z disks as small, basket-like saccules known as **corbular sarcoplasmic reticulum**, a region rich in **Ca^{2+}-release channels** (**junctional feet**) and, therefore, analogous to the SR terminal cisternae of skeletal muscles.
3. **Movement of calcium ions**
   a. During relaxation, **Ca^{2+} leaks** into the sarcoplasm from the sarcolemma at a slow rate via **slow sodium channels** that permit the entry of both Na^+ and Ca^{2+} ions. These channels stay open for an extended period of time (several tenths of a second) resulting in an automatic rhythm of contraction. Ca^{2+} also enters cardiac muscle cells from the extracellular environment via **voltage-gated Ca^{2+} channels** of T tubules.
   b. In response to calcium entering the sarcoplasm, Ca^{2+} is released from the SR and corbular sarcoplasmic reticulum (both via **ryanodine receptors**) to cause contraction of cardiac muscle.
   c. The force of cardiac muscle contraction is directly dependent on the availability of Ca^{2+} in the sarcoplasm. During basal cardiac contraction, only 50% of the available calcium-binding sites of TnC are occupied.
   d. Subsequent to contraction, Ca^{2+} ions are returned into the SR by the activity of an integral sarcoplasmic membrane protein, known as **phospholamban**, which is the primary regulator of the sarcoplasmic Ca^{2+} pump and, thereby, of diastole (relaxation) of the ventricles and atria of the heart.
      (1) In the dephosphorylated state, phospholamban inhibits the sarcoplasmic Ca^{2+} pump.
      (2) When phosphorylated by the action of **cAMP-dependent protein kinase**, phospholamban becomes active and the sarcoplasmic Ca^{2+} pumps open.
4. **Mitochondria** are more abundant in cardiac muscle cells than in skeletal muscle fibers; they lie parallel to the I bands and often are adjacent to lipids.
5. **Atrial granules** are present in the atrial cardiac muscle cells and contain the precursors of **atrial natriuretic peptide** (**ANP**) and **B-type natriuretic peptide** (**BNP**), both of which act to *decrease* resorption of sodium and water in the kidneys, thus decreasing blood volume and, thereby, reducing blood pressure. ANP and BNP act by inhibiting the release of renin from the juxtaglomerular

cells of the kidney and aldosterone from the suprarenal cortex. Additionally, both ANP and BNP hinder vascular smooth muscle contraction, further reducing blood pressure. Ventricular cardiac muscle cells, if stretched much greater than under normal conditions, release both peptides.

6. **Intercalated disks** (Figs. 7.5A, B and 7.6) are complex steplike junctions forming end-to-end attachments between adjacent cardiac muscle cells.

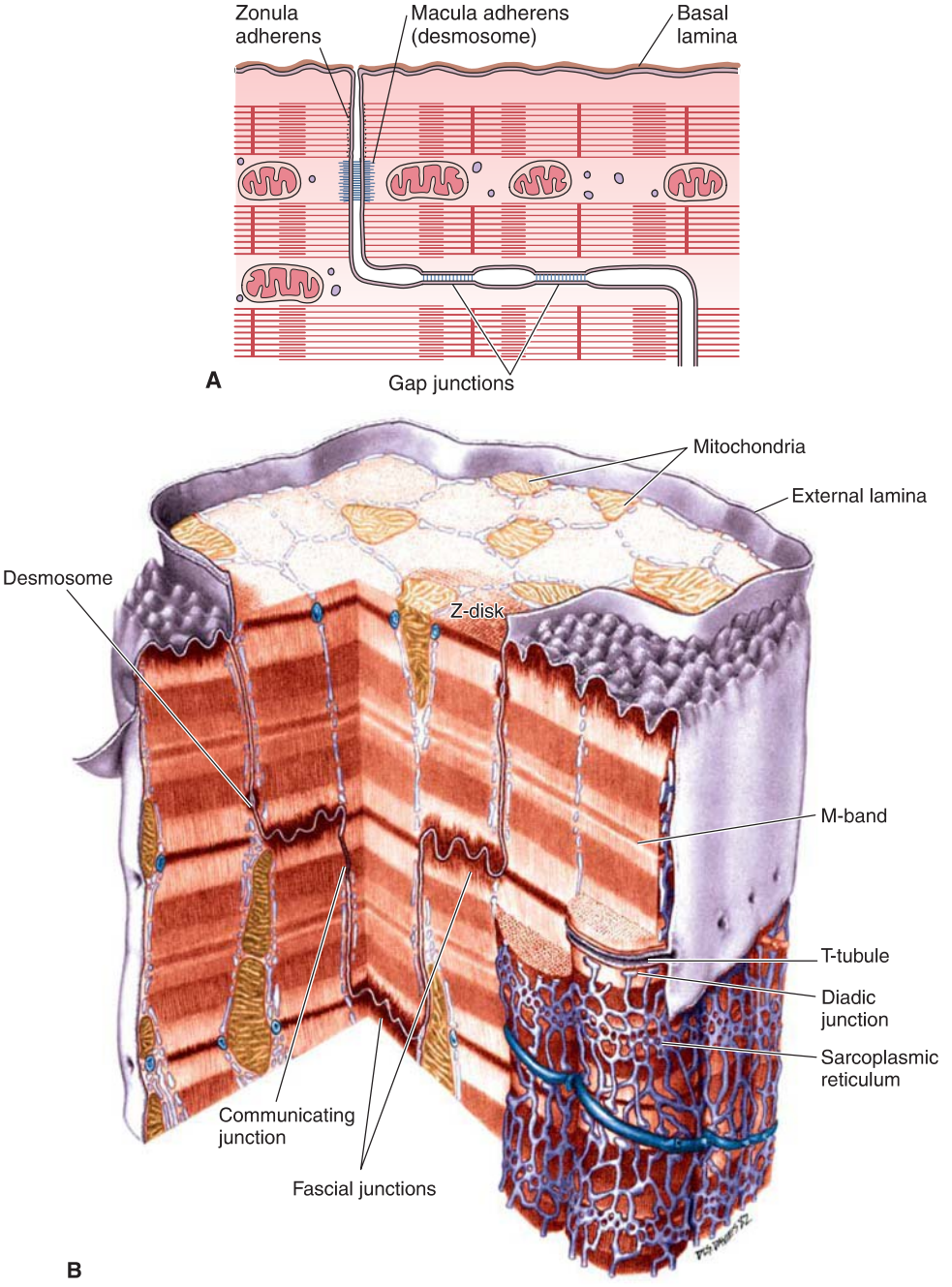


FIGURE 7.5. A. An intercalated disk's two regions, the transverse and lateral portions. **B.** The principal characteristics of intercalated disks are illustrated in this diagram of cardiac muscle cells. The three types of junctions, gap junctions, fascia adherents, and desmosomes, are clearly delineated. Moreover, the relationships between the sarcoplasmic reticulum, T tubule, and the Z-lines of the sarcomeres are also emphasized. (**A:** Adapted with permission from Junqueira LC, Carneiro J, Kelley RO. *Basic Histology*. 8th ed. Norwalk, CT: Appleton & Lange; 1995:197. **B:** Reprinted with permission from Kelly DE, Wood RL, Enders AC. *Bailey's Textbook of Microscopic Anatomy*. 18th ed. Baltimore, MD: Williams & Wilkins; 1984:292.)

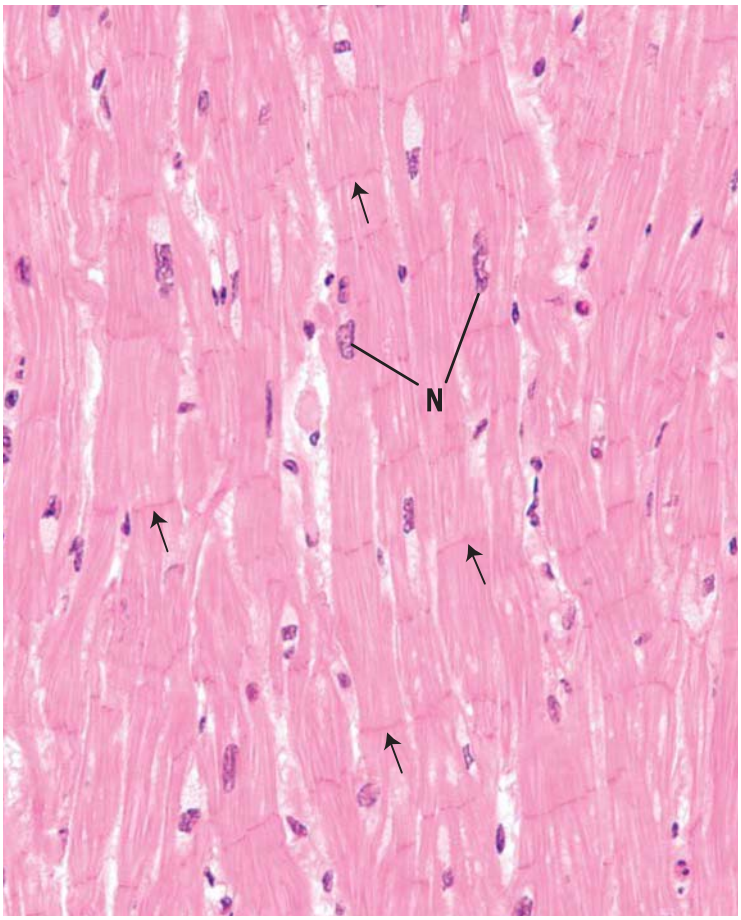


FIGURE 7.6. Light micrograph of a longitudinal section of monkey cardiac muscle fibers. Plastic section (×270). *Arrows*, intercalated disks; N, nuclei of cardiac muscle cells.

   a. The **transverse portion of intercalated disks** runs across muscle fibers at right angles and possesses three specializations: **fasciae adherentes** (analogous to zonula adherentes) to which actin filaments attach, **desmosomes** (macula adherentes), and **gap junctions** (Chapter 3).
   b. The **lateral portion of intercalated disks** has desmosomes and numerous large gap junctions, which facilitate **ionic coupling** between cells and aid in coordinating contraction; thus, cardiac muscle behaves as a **functional syncytium**.

7. Their thin filaments are secured to the Z disk by α-actinin as well as by **nebulette**, a **nebulin-like** molecule that, unlike nebulin in skeletal muscle, extends from the Z disk only as far as the proximal 25% of the length of the thin filament.
8. **Connective tissue elements** support a rich capillary bed that supplies sufficient nutrients and oxygen to maintain the high metabolic rate of cardiac muscle. At least 90% of the energy production of cardiac muscle cells is generated by aerobic respiration.
9. **Purkinje fibers** are **modified** cardiac muscle cells located in the **bundle of His**.
   a. They are specialized for **conduction** and contain a few peripheral myofibrils.
   b. These large, pale cells are rich in glycogen and mitochondria and form gap junctions, fasciae adherentes, and desmosomes with cardiac muscle cells (but not through typical intercalated disks).

CLINICAL CONSIDERATIONS

Although **cardiac muscle cell regeneration** in the adult human was believed said not to occur recent studies performed on tissue sources procured from the Karolinska Institute in Sweden and from the UK Human Tissue Bank in Great Britain, based on the ^{14}C levels in the DNA of heart muscles of individuals who were born before the nuclear bomb testing began, showed otherwise. Approximately 1% of heart muscle fibers of 20-year-old individuals and almost 50% of the cardiac muscle cells of 50-year-old individuals were formed after these individuals were born.

Myocardial infarct is an irreversible necrosis of cardiac muscle cells because of prolonged ischemia (ischemia lasting for more than approximately 20–40 minutes). Almost immediately after the lack of oxygen—mostly because of blockage of a coronary artery or its branches—oxygen-deprived cardiac muscles switch from aerobic to anaerobic glycolysis. Unfortunately, anaerobic glycolysis does not produce enough ATP or creatine phosphate for normal functioning of the affected heart muscle cells, and the situation is further exacerbated by the accumulation of lactic acid and other noxious substances. Within a minute or so of complete ischemia, the affected cardiac muscle cells exhibit a drastic reduction in contractility. If a large enough number of cells are affected, the patient can experience acute heart failure. However, if the individual receives treatment within 30 minutes or so and the ischemia is reversed, most cardiac myocytes can recover and the patient's life can be saved. After a period of 2 to 4 hours of incomplete but still severe ischemia, most of the cells affected will die and that region of the heart will no longer be able to function. Dying and dead cardiac muscle cells release creatine phosphokinase, creatine phosphokinase MB isoenzyme, and cardiocyte-specific TnI, and these three substances—especially the last—are indicative of a myocardial infarct, a condition that may result in death if the cardiac muscle damage is extensive.

Cardiomyopathies are diseases of cardiac muscle that are caused by abnormalities of the cell, rather than from ischemia. Late in pregnancy or early in the postpartum period, a condition known as **peripartum cardiomyopathy** may occur. The cause of this condition is not understood, but it is believed to have multiple causes rather than a single cause. Some of the causes may be elevated blood pressure during pregnancy, nutritional deficiency, immune reaction, or other metabolic disturbances.

VI. SMOOTH MUSCLE

A. **Structure—smooth muscle cells (Figs. 7.7 and 7.8; Table 7.3).** Smooth muscle cells are **nonstriated**, **fusiform** cells that range in length from 20 μm in small blood vessels to 500 μm in the uterus of pregnant women. They contain a single nucleus and actively divide and **regenerate**. They are surrounded by an external lamina and a reticular fiber network and may be arranged in layers, small bundles, or helices (in arteries).

1. **Nucleus**
   a. The centrally located **nucleus** may not be visible in each cell in cross sections of smooth muscle because some nuclei lie outside the plane of section.
   b. The nucleus in longitudinal sections of contracted smooth muscle can have a **corkscrew shape** and is **deeply indented**.
2. **Cytoplasmic organelles**
   a. **Mitochondria**, **RER**, **and the Golgi complex** are concentrated near the nucleus and are involved in the synthesis of type III collagen, elastin, glycosaminoglycans, external lamina, and growth factors.
   b. **Sarcolemmal vesicles** (**caveolae**), present along the periphery of smooth muscle cells, may function in the uptake and release of Ca^{2+}. **SER** is sparse and may be associated with caveolae.
3. **Filaments in smooth muscle**
   a. **Contractile filaments** (**actin and myosin**) are **not** organized into myofibrils. They are attached to peripheral and cytoplasmic densities and aligned obliquely to the longitudinal axis of smooth muscle cells.
      (1) **Thick filaments** (composed of **myosin II**) are each surrounded by as many as 15 thin filaments. In contrast to striated muscle, the heads of the myosin molecules all point in

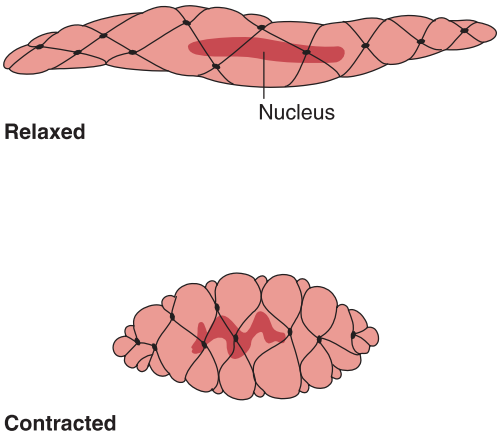


FIGURE 7.7. Relaxed and contracted smooth muscle cells: cytoplasmic and peripheral densities. The nucleus of the smooth muscle cell assumes a corkscrew shape. (Adapted with permission from Gartner LP. *Textbook of Histology*. 4th ed. Philadelphia, PA: Elsevier; 2017.)

the same direction. Prior to contraction the myosin II molecule is **inactive** and cannot bind to the actin filament because the tail of the myosin molecule (light meromyosin) is attached to the heavy meromyosin, so that the molecule resembles a golf club whose handle is folded to contact its head.

(2) **Thin filaments** are composed of **actin**, **caldesmon**, **tropomyosin**, and **calponin**. Caldesmon functions similarly to TnT and TnI in that, in concert with tropomyosin, it masks the sites where myosin binds to effect muscle contraction.

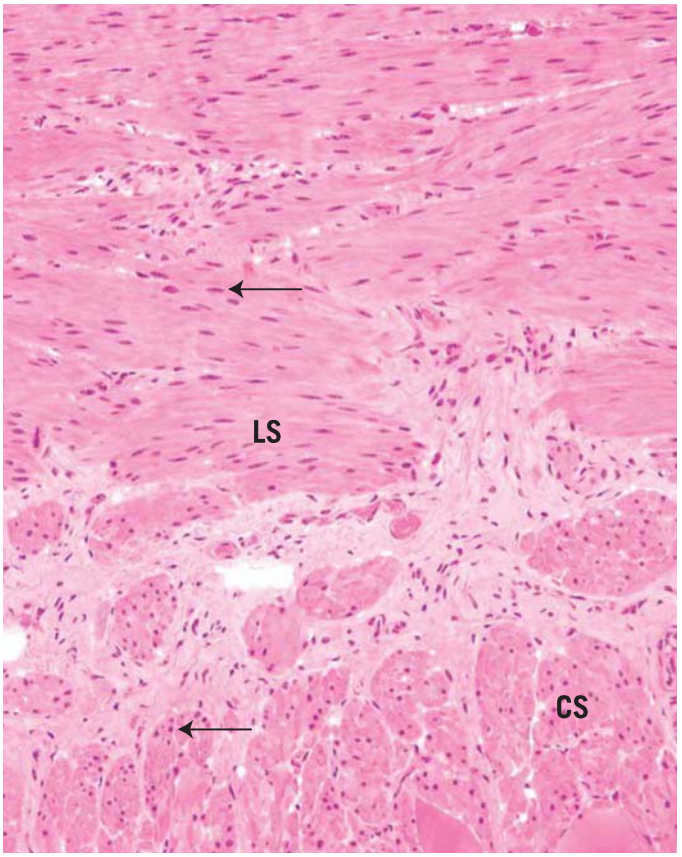


FIGURE 7.8. Light micrograph of a longitudinal section and cross-section of smooth muscle cells from the monkey duodenum. Plastic section (×270). *Arrows*, nuclei of smooth muscle cells; CS, cross-section of smooth muscle fibers; LS, longitudinal section of smooth muscle fibers.

   b. Intermediate filaments are attached to cytoplasmic densities and include **vimentin** and **desmin** in **vascular** smooth muscle cells and **desmin** only in **nonvascular** smooth muscle cells.
4. **Cytoplasmic densities**, believed to be **analogous to Z disks**, contain α-actinin and various Z-disk-associated proteins and function as **filament attachment sites**.
5. **Gap junctions** between smooth muscle cells facilitate the spread of excitation. These gap junctions are collectively called the **nexus**.

B. Contraction of smooth muscle occurs more slowly and lasts longer than contraction of skeletal muscle because the rate of ATP hydrolysis is slower. Contraction of smooth muscle is regulated by a different mechanism from that of skeletal muscle contraction.

1. The **contraction cycle** is stimulated by a transient increase in cytosolic Ca^{2+}.
   a. Ca^{2+} binds to **calmodulin**, altering its conformation.
   b. The Ca^{2+}–calmodulin complex activates the enzyme **myosin light-chain kinase**, which catalyzes phosphorylation of one of the light chains, the **regulatory light chain**, of myosin.
   c. Phosphorylated regulatory light chain of myosin permits the myosin molecule to unfold so that it can interact with other myosin II molecules to form a thick filament.
   d. In the presence of Ca^{2+}, the inhibitory effect of the **caldesmon–tropomyosin complex** on actin–myosin interaction is eliminated (caldesmon, in concert with tropomyosin, masks the active site of G-actin). Another inhibitor of contraction is **calponin**, which, when phosphorylated, loses its inhibitory capability.
   e. The globular head of phosphorylated myosin interacts with actin and stimulates myosin ATPase, resulting in **contraction**. As long as myosin is in its phosphorylated form, the contraction cycle continues.
   f. **Dephosphorylation** of myosin disturbs the myosin–actin interaction and leads to relaxation.
2. **Initiation of contraction**
   a. In **vascular smooth muscle**, contraction is usually triggered by a **nerve impulse**, with little spread of the impulse from cell to cell.
   b. In **visceral smooth muscle**, it is triggered by stretching of the muscle itself (**myogenic**); the signal spreads from cell to cell.
   c. In the **uterus** during labor, it is triggered by **oxytocin**.
   d. In smooth muscle elsewhere in the body, it is triggered by **epinephrine**.

C. Innervation of smooth muscle is by *sympathetic* (noradrenergic) nerves and *parasympathetic* (cholinergic) nerves of the autonomic nervous system, which act in an antagonistic fashion to stimulate or depress activity of the muscle.

CLINICAL CONSIDERATIONS

Leiomyoma is a benign neoplasm of smooth muscle. It is frequently present in the uterus where it forms the most common benign tumor in women. Additional locations commonly involved are the nipples of the breast, arrector pili muscles of the skin (pilar leiomyomas), labia majora of the female, and scrotum in the male (genital leiomyomas). Generally, leiomyomas are small individual tumors, less than an inch in size, that only occasionally display mitotic figures. They consist of bundles of spindle-shaped cells that appear to be situated perpendicular to each other. Surgical excision is the normal treatment unless the tumors—especially in the skin—are too numerous to remove.

Leiomyosarcomas are compact, painless, malignant tumors of smooth muscle. They are more common in adult females than in males and compose almost 20% of sarcomas of noncalcified tissues. Their normal locations are the skin, deep tissues of the arms and legs, and in the retroperitoneal soft tissues of the abdominal cavity. They are composed of groups of spindle-shaped cells that closely resemble smooth muscle cells. Leiomyosarcomas of the skin and extremities are small and easily treated, but those located retroperitoneally are usually very large because they are detected late in the progression of the cancer and have metastasized to such an extent that the prognosis is poor.

VII. CONTRACTILE NONMUSCLE CELLS

A. Myoepithelial cells

1. In certain glands, these cells share basal laminae of secretory and duct cells and are attached to the underlying basal lamina via hemidesmosomes.
2. Although generally similar in morphology to smooth muscle cells, they have a **basketlike shape** and several radiating **processes**; they arise from **ectoderm** and can **contract** to express secretory material from glandular epithelium into the ducts and out of the gland.
3. They contain **actin**, **myosin**, and intermediate filaments as well as cytoplasmic and peripheral densities to which these filaments attach.
4. Contraction is similar to that of smooth muscle and occurs via a **calmodulin-mediated process**. In lactating **mammary glands**, they contract in response to **oxytocin**. In **lacrimal glands**, they contract in response to **ACh**.

B. Myofibroblasts

1. Unlike myoepithelial cells, **myofibroblasts** arise from mesenchymal cells and possess vimentin as their characteristic intermediate filaments as well as caldesmon and cytokeratins.
2. Although they resemble fibroblasts, they possess higher amounts of **actin** and **myosin** and are capable of **contraction** as during wound healing to decrease the size of the defect (**wound contraction**).

Review Test

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 19-year-old male patient and his mother arrive in the emergency department, both with nausea, vomiting, and visual disorders. The physician taking their history notes that they both had canned green beans that tasted funny. Which of the following possibilities should the physician consider?

(A) DMD
(B) ALS
(C) Botulism
(D) Myasthenia gravis
(E) Myocardial infarct

Questions 2 and 3 refer to the following scenario:

A forensic pathologist is called to the scene of a crime where a middle-aged white male was found dead as a result of stabbing. The body was in an apartment with normal room temperature. Rigor mortis of the face and neck was complete but that of the extremities was incomplete.

2. Which muscles enter rigor mortis first?

(A) Muscles of the hands
(B) Muscles of the thigh
(C) Muscles of the forearm
(D) Muscles of the face
(E) Muscles of the feet

3. Approximately how many hours have elapsed since the patient died?

(A) 2
(B) 5
(C) 13
(D) 60
(E) 75

Questions 4 through 6 refer to the following scenario:

A 65-year-old male patient complains to his internist about weakness in the muscles of his face, arms, and legs. He also complains about recurrent respiratory infections.

4. What should the internist suspect?

(A) Botulism
(B) Muscular dystrophy
(C) ALS
(D) Leiomyoma
(E) Myasthenia gravis

5. Which structure should be examined for an increase in size?

(A) Thymus
(B) Thyroid
(C) Parotid gland
(D) Liver
(E) Testes

6. Blood chemistry should look for antibodies against which of the following?

(A) ACh receptors
(B) Thyroglobulin
(C) Thymosin
(D) Catecholamine receptors
(E) Adrenergic receptors

7. A young female patient presents with a 1-cm-long tumor on her forearm. The dermatologist excises it. The pathology report indicates the presence of bundles of spindle-shaped cells that are arranged perpendicular to each other. The cells display occasional mitotic figures. What is the most probable diagnosis?

(A) DRM
(B) Leiomyosarcoma
(C) Muscular dystrophy
(D) Leiomyoma
(E) Myasthenia gravis

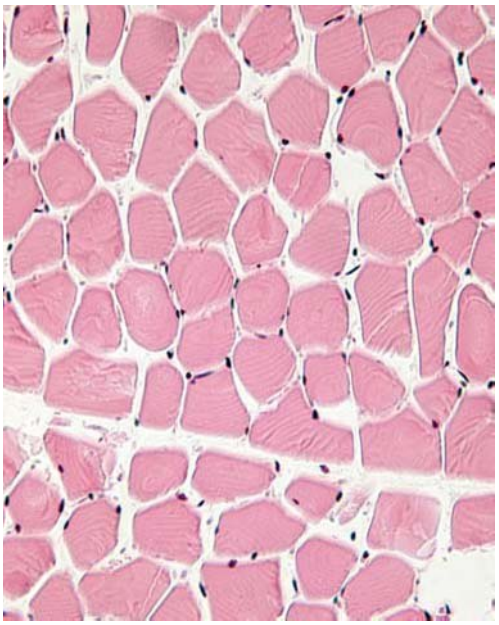
8. A patient who was diagnosed with ALS died and the histopathology indicated that he had a decrease in the population of motoneurons in the ventral horn of his spinal cord. He also displayed a decrease in the motoneurons in the nuclei of which one of the following cranial nerves?

(A) CN III (oculomotor)
(B) CN IV (trochlear)
(C) CN V (trigeminal)
(D) CN VI (abducens)
(E) CN VII (facial)

9. Which of the following is true for cardiac muscle?

(A) T tubules are located at the Z disk.
(B) T tubules have a smaller diameter than those of skeletal muscle.
(C) Troponin is absent.
(D) It possesses triads.
(E) Oxytocin triggers contraction.

Question 10 is based on the following photomicrograph:



10. This is a normal region of a biopsy of a deep muscle of the thigh of a 25-year-old patient who succumbed to the disease. What was the name of the disease?

(A) FSHMD
(B) Rhabdomyosarcoma
(C) Myocardial infarct
(D) Cardiomyopathy
(E) Leiomyosarcoma

Answers and Explanations

1. **C.** Of the possibilities listed, botulism is the only possible consideration, especially because they both had canned food. DMD is most common in young men but very rare in older women. It would be highly unlikely that both mother and son would show symptoms of ALS or myasthenia gravis or have myocardial infarct at the same time.
2. **D.** Muscles of the face and neck reach rigidity first following death.
3. **B.** Approximately 5 hours have elapsed since the individual was killed. The reasoning is that the muscles of the face were completely rigid, so the myofilaments have not started to decompose; therefore, the incomplete rigidity of the muscles of the extremities was not due to decomposition of the myofilaments but due to the fact that peak rigidity has not been reached. At room temperature, muscles of the extremities reach rigidity 4 to 6 hours after death.
4. **E.** The internist should suspect myasthenia gravis because of the symptoms as well as the gender and age of the patient.
5. **A.** The thymus of patients with myasthenia gravis is usually enlarged or exhibits thymoma.
6. **A.** The internist should look for antibodies against ACh receptors because myasthenia gravis is an autoimmune disease where the immune system manufactures antibodies against its own ACh receptors.
7. **D.** The pathology report and the size and location of the tumor indicates that the patient has leiomyoma, a condition characterized by small tumor with bundles of spindle-shaped cells arranged perpendicular to each other.
8. **C.** The number of motoneurons decreases in patients with ALS in their trigeminal (CN V), nucleus ambiguus [glossopharyngeal (CN IX), vagus (CN X), accessory (XI)], and hypoglossal (CN XII) motor nuclei.
9. **A.** The T tubules of cardiac muscle cells are wider than those of skeletal muscle cells and are lined by external lamina (a basal lamina–like material). In contrast to skeletal muscle, the T tubules are located at the Z disk, where they often form dyads, not triads.
10. **B.** Because this is a cross-section of skeletal muscle of a young male, the answer has to be rhabdomyosarcoma. FSHMD is also a skeletal muscle condition, but it does not impact the length of life of the patient. The other three conditions listed involve cardiac and smooth muscles, thus those distracters are incorrect.

chapter 8

Nervous Tissue

I. OVERVIEW—NERVOUS SYSTEM

The nervous system, composed of all the nervous tissue elements of the body, can be studied from numerous perspectives, namely by its anatomical, functional, and cellular characteristics.

A. Anatomically, **it may be divided into the *central nervous system* (*CNS*), which includes the brain and spinal cord encased in the skull and vertebral column, and the *peripheral nervous system* (*PNS*), which includes the nerves outside the CNS and their associated ganglia as well as connections to the CNS including the receptors and motor components of the peripheral nerves of the body.** However, it must be stressed that the two subdivisions are physically continuous with each other.

B. Functionally, **it may be divided into a *sensory* component, which transmits electrical impulses (signals) from the periphery to the CNS, and a *motor* component, which transmits impulses** from **the CNS to the periphery, that is, to various structures of the body.** The motor component is further divided into the **somatic** and **autonomic** systems.

1. The **somatic nervous system** (**SNS**) located within both the CNS and PNS controls sensory and motor functions of all conscious voluntary actions. However, it does not control functions related to smooth muscles, cardiac muscles, reflex arcs, or glands.
2. The **autonomic nervous system** (**ANS**) functions to regulate the internal organs of the body.
   a. It is further subdivided into the **sympathetic**, **parasympathetic**, and **enteric nervous systems**. The sympathetic nervous system readies the body for action against hostile situations resulting in "flight or fight or freeze," whereas the parasympathetic nervous system is "calming" and supplies secretomotor innervation to most exocrine glands.
   b. The enteric nervous system, a very large component of the ANS, serves the digestive system. Although it operates independently, both the sympathetic and parasympathetic components have the ability to modulate the functions of the enteric system.

C. Nervous tissue contains two types of cells: ***nerve cells* (*neurons*), which conduct electrical impulses, and supporting cells, which support, nurture, and protect the neurons within the CNS (*glial* [*neuroglial*] *cells*) as well as cells located in the PNS (*satellite cells*, *capsule cells*, and *Schwann cells*).**

II. NERVOUS SYSTEM HISTOGENESIS (Fig. 8.1)

A. **A region of the ectoderm thickens and differentiates into *neuroepithelium* and forms the neural plate, which invaginates to form a midline depression called the *neural groove*, flanked by the *neural folds*.**

B. The neural tube, **a cylindrical structure that results from fusion of the edges of the neural folds, enlarges at its cranial end to form the *brain*.** The remaining portion gives rise to the **spinal cord.**

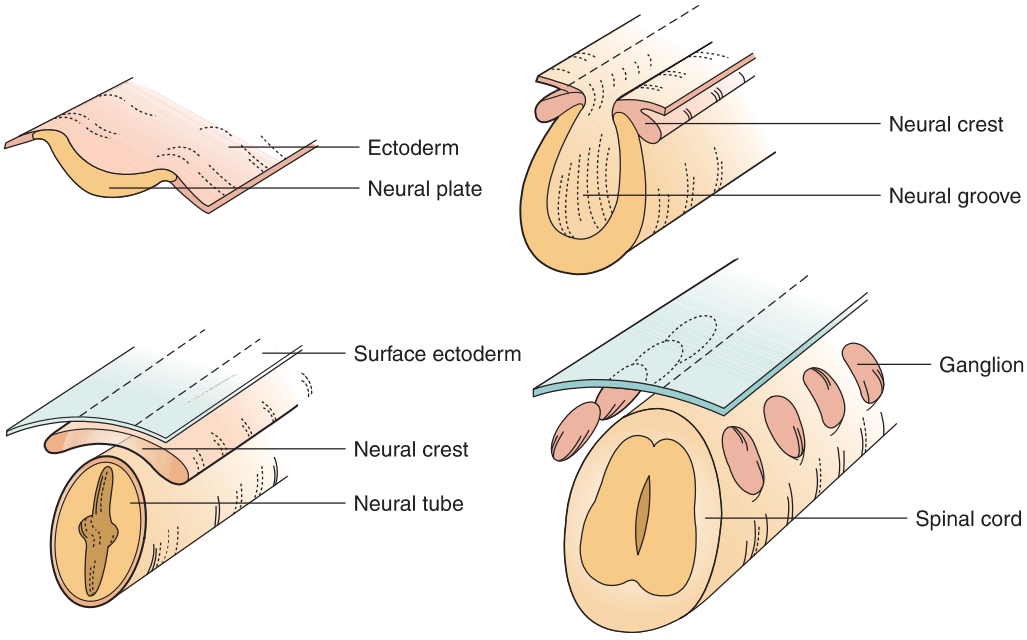


FIGURE 8.1. Early histogenesis of the nervous system. Notice how the neural crest forms and then fragments to migrate to its destinations.

C. **Neural crest cells stream off the edges of the neural folds before formation of the neural tube.** These cells migrate throughout the body and give rise to the following structures: sensory neurons of cranial and spinal sensory ganglia; the majority of sensory neurons and Schwann cells of the PNS; all enteric and autonomic ganglia and their postganglionic neurons and associated glia; the majority of the mesenchymal (ectomesenchymal) cells of the head and anterior portion of the neck; all melanocytes of the skin and oral mucosa; odontoblasts (cells responsible for the production of dentin of the tooth); cells of the arachnoid and pia mater (that are rostral to the mesencephalon); and chromaffin cells of the adrenal medulla.

CLINICAL CONSIDERATIONS

Abnormal histogenesis of the CNS results in congenital malformations.

1. **Spina bifida** is a defective closure of the spinal column. In severe cases, the spinal cord and meninges may protrude through the unfused areas. Very severe cases may be associated with defective development of the viscera of the thorax and abdomen.
2. **Anencephaly** is failure of the developmental anterior neuropore to close. This produces a poorly formed brain without a cranial vault. It is usually not compatible with life.
3. **Hirschsprung disease** (**congenital aganglionic megacolon**) is the result of abnormal organogenesis in which neural crest cells fail to migrate into the wall of the gut. The disease is characterized by the **absence of Auerbach plexus**, a part of the parasympathetic system innervating the distal segment of the colon. This loss of motor function leads to uncoordinated peristaltic movement of the affected colon resulting in severe dilation of the proximal, unaffected colon and in constipation.
4. **Neuroglial tumors** constitute 50% of intracranial tumors. CNS tumors are rarely associated with neurons; they are mostly derived from neuroglial cells (e.g., astrocytes, oligodendrocytes, and ependymocytes). These tumors range in severity from slowly growing **benign oligodendrogliomas** to rapidly growing fatal **malignant astrocytomas.**
5. Brains of patients with AIDS and HIV-1 possess large populations of **microglial cells**. Although microglia of these individuals do not attack their neurons, they produce cytokines that are toxic to them.

III. NERVOUS SYSTEM CELLS

A. Neurons consist of a *cell body* (*soma, perikaryon*), and its processes, which usually include multiple *dendrites* and a single *axon*. Neurons comprise the smallest and largest cells of the body, ranging from 5 to 150 μm in diameter.

1. **Morphologic classification of neurons** (Fig. 8.2)
   a. **Bipolar neurons** possess a single axon and a single dendrite. These neurons are present in some sensory organs (e.g., the vestibular–cochlear system).
   b. **Multipolar neurons** possess a single axon and more than one dendrite. These neurons are the **most common type** of neuron in vertebrates.
   c. **Pseudounipolar neurons** (known as **unipolar neurons** because true unipolar neurons, that is, neurons with a single process, are very rare in vertebrates) possess a single process that extends from the cell body and subsequently branches into an axon and dendrite. They originate embryologically as bipolar cells whose axon and dendrite fuse into a single process functionally categorized as an axon. They are present in spinal and cranial ganglia.

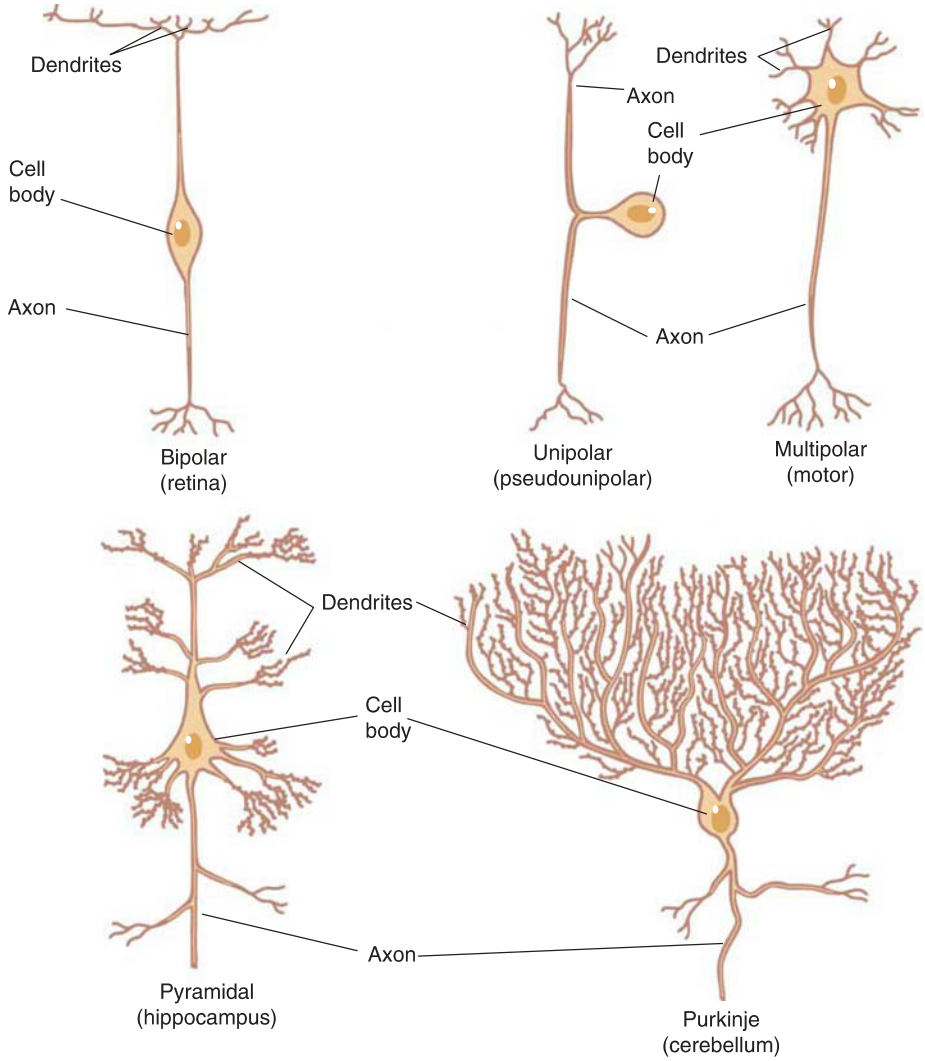


FIGURE 8.2. Various types of neurons. (Reprinted with permission from Gartner LP. *Textbook of Histology*. 4th ed. Philadelphia, PA: Elsevier; 2017.)

2. **Functional classification of neurons**
   a. **Sensory neurons** receive stimuli from the internal and external environments and conduct impulses ***to the CNS*** for processing and analysis.
   b. **Interneurons** (**intercalated neurons**) connect other neurons in a chain or sequence. They commonly connect sensory and motor neurons; they also regulate signals transmitted to neurons.
   c. **Motor neurons** conduct impulses ***from the CNS*** to other neurons, muscles, and glands.
3. **Neuron structure** (Figs. 8.3 and 8.4): Neurons possess a **cell body** and **processes**, known as **dendrites** and **axons**.
   a. The **cell body** (**soma**, **perikaryon**) is the region of a neuron that houses the large, spherical, pale-staining, centrally located **nucleus**; majority of cytoplasmic organelles, namely **polysomes** and **rough endoplasmic reticulum** (RER; **Nissl bodies**), **Golgi complex**, and **mitochondria**; inclusions, such as **melanin-containing granules**, **lipofuscin-containing granules**, and **lipid droplets**; and cytoskeletal elements, specifically, intermediate filaments known in neurons as **neurofilaments** (10 nm in diameter), **microtubules** (24 nm in diameter), and the plasmalemma-associated **microfilaments** (**actin filaments** 6 nm in diameter).
   b. **Dendrites receive stimuli** (signals) from sensory cells, axons, or other neurons and convert these signals into small electrical impulses (action potentials) that are **transmitted toward** the soma.
      (1) The cytoplasm of dendrites is similar to that of the soma except that it lacks a Golgi complex, near the dendritic terminals.
      (2) Dendrites possess **arborized terminals** where mitochondria are abundant, whereas other organelles are reduced in number or are absent; the multitude of terminals permit a neuron to receive stimuli simultaneously from many other neurons.
      (3) Spines on the surface of dendrites increase the surface area available for synapse formation with other neurons.

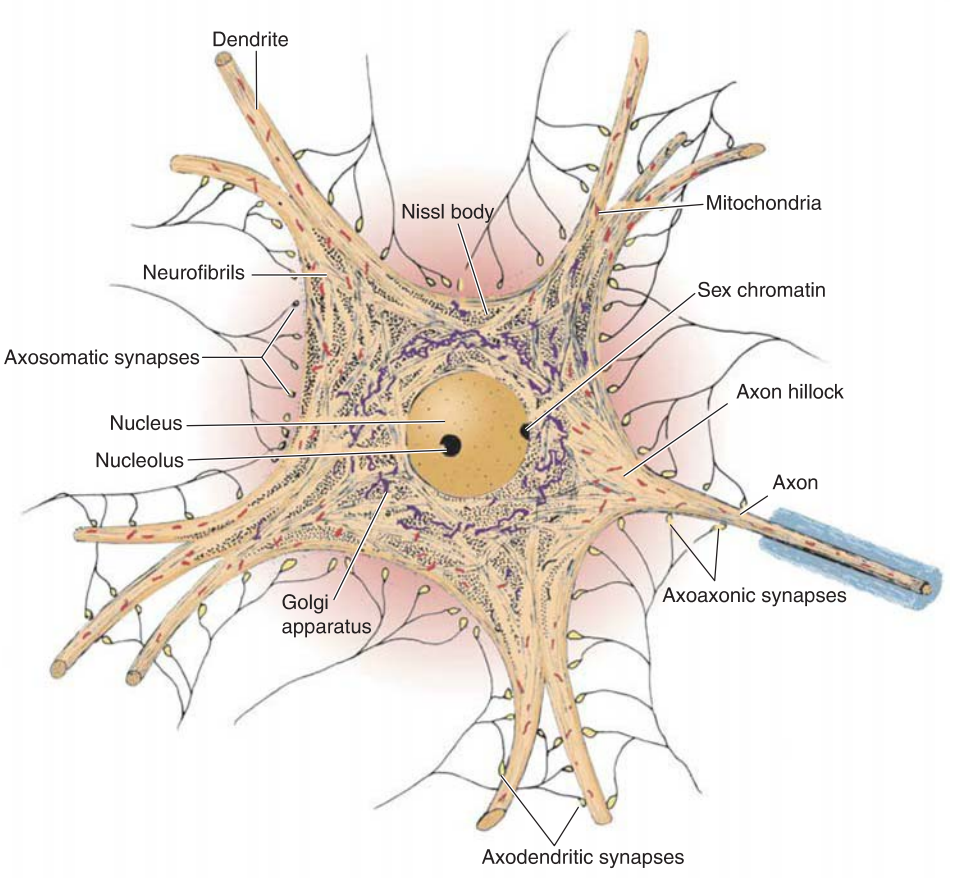


FIGURE 8.3. A typical neuron with its constituents and synapses. (Reprinted with permission from Kiernan JA. *Barr's The Human Nervous System: An Anatomical Viewpoint.* 8th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2005:19.)

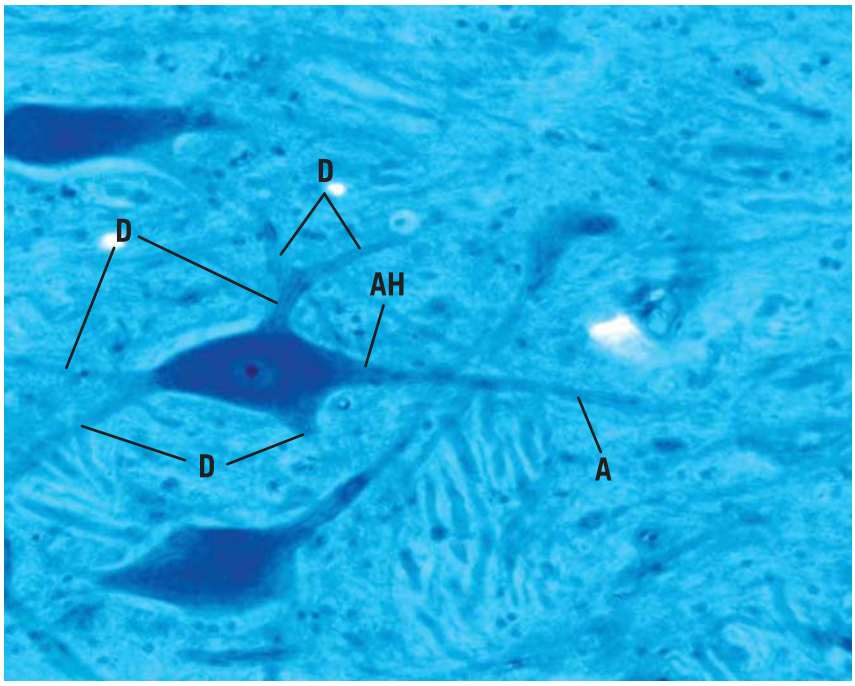


FIGURE 8.4. Light micrograph of the spinal cord in cross-section (×540). Observe the multipolar neurons in the ventral horn of the spinal cord. A, axon; AH, axon hillock; D, dendrites.

CLINICAL CONSIDERATIONS

Dendritic spines diminish with age and poor nutrition and exhibit altered configurations in individuals with trisomy 21 or trisomy 13.

c. **Axons conduct impulses** without any diminution in their strength **away from** the soma to small branches (**axon terminals**) from which impulses are passed to another neuron or other types of cells. Axons may have **collaterals**, branching at right angles from the main trunk.
   (1) The diameter and length of axons in different types of neurons vary. Some axons may be 100 cm in length.
   (2) Axons originate from the **axon hillock**, a specialized region of the soma that lacks RER, ribosomes, Golgi cisternae, and Nissl bodies but contains many microtubules and neurofilaments (whose abundance may regulate neuron diameter).
   (3) Axon cytoplasm (**axoplasm**) lacks a Golgi complex but contains smooth endoplasmic reticulum (SER), RER, and elongated mitochondria.
   (4) A plasma membrane surrounding the axon is called the **axolemma**.

CLINICAL CONSIDERATIONS

Alzheimer disease is the most common cause of dementia. It is the sixth leading cause of death in the United States and is considered to be a disease of the aged. Currently, about 5.2 million persons in the United States have been diagnosed with Alzheimer disease, of whom 5 million are 65 or older, but 200,000 are younger than 65 years of age. In 2013, Alzheimer disease was estimated to cost the United States $203 billion, which is expected to rise to $1.2 trillion by 2050.

Alzheimer disease starts with memory loss and confusion, loss of finding words and of abstract thinking, disorientation, and depression, followed by irritability and mood swings accompanied by aggressive behavior. Finally, withdrawal, decline of the senses, and loss of bodily functions occur.

A combination of genetics, lifestyle, and the environment seems to play a role in triggering the onset. The disease is characterized by the loss of neurons and synapses mainly within the cerebral cortex followed by atrophy of the individual cerebral lobes as well as the development of β-amyloid plaques and neurofibrillary tangles that probably render those neurons nonfunctional. Indirect evidence in recent studies has shown that β-amyloid protein can act as a prion and be transferred from infected neurons to noninfected neurons by traveling down the axon of the infected cell and enter the uninfected cell via synapses. Apparently, eight young patients were treated with growth hormone that was tainted with prions, and they died between 36 and 51 years of age of Creutzfeldt–Jakob disease. Autopsy of their brains demonstrated the presence of β-amyloid protein, suggesting the early presence of Alzheimer disease.

Still other investigations suggest that Alzheimer disease is a neuroendocrine disorder, specifically **type 3 diabetes mellitus**, resulting from specific deficiencies in the production of insulin, insulin-like growth factor-1, and insulin-like growth factor-2 as well as in the scarcity of receptors for these three molecules confined to certain regions of the brain.

Recently, a new monoclonal antibody, **aducanumab**, has been tested and has been shown to be capable of crossing the blood–brain barrier and binding to aggregated forms of β-amyloid plaques, forming complexes with them that are cleared by microglia. PET amyloid imaging has shown that, at high doses, aducanumab nearly eliminates β-amyloid from the brain. Although the study is still in clinical trials, it has shown that the decline in mental skills in patients on the monoclonal antibody has been slowed.

B. The neuroglial cells, astrocytes and oligodendroglia, microglia, and ependymal cells, are located only in the CNS. Schwann cells and capsule cells are present only in the PNS.

1. **General characteristics.** Neuroglial cells comprise several cell types and outnumber neurons by approximately a factor of 10. They function to **support** and **protect neurons** and appear to provide some regulation of neurons in the process of neural transmissions; however, they do not conduct impulses or form synapses with other cells. Moreover, neuroglia actively monitor synapses, removing neurotransmitter molecules from synapses and delivering molecules known as **gliotransmitter substances**, such as glutamate and adenosine triphosphate (ATP), into the synaptic vicinity. These gliotransmitters appear to suppress synaptic transmission in cultured hippocampal neurons. Additionally, neuroglial cells possess the capacity to undergo cell division.
2. **Types of neuroglial cells** (Fig. 8.5 and Table 8.1). Note that Schwann cells are also discussed in this section but they are present only in the PNS.
   a. **Astrocytes** are of two types: **Protoplasmic astrocytes** reside mostly in gray matter and have branched processes that envelop blood vessels, neurons, and synaptic areas. They contain intermediate

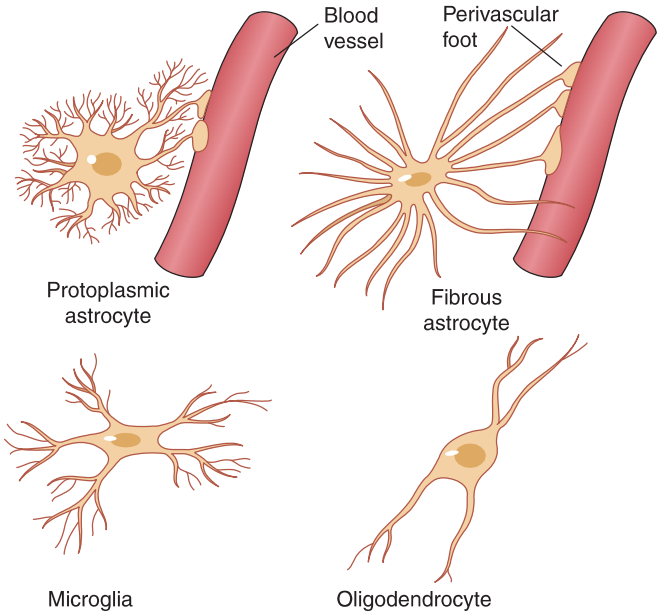


FIGURE 8.5. Various types of neuroglial cells. (Adapted with permission from Gartner LP. *Textbook of Histology*. 4th ed. Philadelphia, PA: Elsevier; 2017.)

table 8.1 Neuroglia and Their Properties

Neuroglia	Location	Function
Protoplasmic astrocytes	Gray matter of CNS	Support and isolate neurons; sequester Na^+ ions; metabolize extracellular neurotransmitters; repair damage to CNS by forming glial scar tissue; surround unmyelinated axons; form a protective **sealed barrier** between the pia mater and the nervous tissue of the brain and the spinal cord; regulate CSF flow through the gray matter so that during sleep CSF flow is increased by about 50% thus cleansing the interstitial spaces of waste products and excess neurotransmitters; in the embryo, they establish pathways along which neurons migrate
Fibrous astrocytes	White matter of CNS	Sequester Na^+ ions; metabolize extracellular neurotransmitters; repair damage to CNS by forming glial scar tissue; surround unmyelinated axons; in the embryo, they establish pathways along which neurons migrate
Oligodendroglia	Mostly white matter but also in gray matter of CNS	In white matter they form myelin sheaths around axons of the CNS; in gray matter they surround neurons; live symbiotically with neurons
Microglia	Both gray and white matter of CNS	Phagocytose damaged nerve tissue in the CNS; secrete cytokines that attract T cells to the site of injury; possess the ability to become antigen-presenting cells and present the antigens to the newly arrived T cells
Ependymal cells	Lining ventricles of the brain and central canal of spinal cord	Promote movement of CSF; form simple cuboidal epithelium of the choroid plexus; in the third ventricle differentiate to form tanycytes
Schwann cells	PNS only	Myelinate axons and surround unmyelinated axons of the PNS; function during degeneration and regeneration of axons

CNS, central nervous system; CSF, cerebrospinal fluid; PNS, peripheral nervous system.

filaments composed of **glial fibrillar acidic protein** (**GFAP**). They not only help in establishing the **blood–brain barrier** but may also contribute to its maintenance. **Fibrous astrocytes** reside mostly in **white matter** and have long, slender processes with few branches. They also contain many intermediate filaments composed of **GFAP**.

(1) Generally speaking, astrocytes are the largest of the neuroglial cells that reside in the CNS. They have many processes, some of which possess expanded pedicles (**vascular feet**) that surround blood vessels, whereas others exhibit processes that contact the pia mater.

(a) They scavenge ions and debris from neuron metabolism and supply energy for metabolism; provide **structural support** for nervous tissue; and proliferate to form **scar tissue** (**glial scar**) after injury to the CNS.

(b) Along with other components of the neuroglia, astroglia form a protective **sealed barrier** between the pia mater and the nervous tissue of the brain and the spinal cord.

b. Oligodendrocytes

(1) Oligodendrocytes, located in both **gray matter** and **white matter**, are neuroglial cells that possess a small, round, condensed nucleus and only a few short processes and their electron-dense cytoplasm contains ribosomes, numerous microtubules, many mitochondria, RER, and a large Golgi complex. They live **symbiotically** with neurons (i.e., each cell type is affected by the metabolic activities of the other). These cells are necessary for the survival of neurons in the CNS.

(2) Oligodendrocytes produce **myelin**, a lipoprotein material organized into a sheath that insulates and protects axons in the CNS. Each oligodendrocyte forms several processes and each process produces myelin for a single internode for a single axon. In this manner, an oligodendroglion can myelinate an internode for several axons.

c. Microglia are small, **phagocytic** neuroglial cells that are derived from the mononuclear phagocytic cell population in the bone marrow. They have a condensed, elongated nucleus and many short, branching processes. Normally they are inactive but during injury or pathogen invasion they release **interferon-γ**, which activates neighboring microglia. Activated microglial cells remove residues of cellular injury and secrete cytokines that **attract T cells** to the site of injury. Microglia also possess the ability to become **antigen-presenting cells** and present the antigens to the newly arrived T cells.

d. Ependymal cells, derived from the neuroepithelium, are the **epithelial cells** that line the neural tube and ventricles of the brain. In certain regions of the brain, they possess **cilia**, which aid in moving the cerebrospinal fluid (CSF). Modified ependymal cells contribute to the formation of the **choroid plexus**.

e. Schwann cells

(1) Schwann cells, derived from neural crest cells, are located only in the PNS. They are flat cells with only a few mitochondria and a small Golgi region.

(2) These cells perform the same function in the PNS as oligodendrocytes in the CNS: They protect and insulate neurons. Schwann cells form either unmyelinated or myelinated coverings over axons. However, a single Schwann cell can only insulate a single axon, whereas a single oligodendrocyte may insulate several axons. A myelin sheath consists of plasmalemmae of copious numbers of Schwann cells wrapped around a **single axon**.

(3) **Unmyelinated peripheral nerve fibers** are surrounded by a large number of Schwann cells where each segment of the axon is enveloped by a single Schwann cell. Several axon segments may be embedded in each Schwann cell (Fig. 8.6F). Because impulses in myelinated axons jump from one node of Ranvier to another node of Ranvier and in unmyelinated axons they move sequentially from ion channel to ion channel, propagation of the impulse is much faster in myelinated axons. Interestingly, unlike in the PNS, CNS unmyelinated axons are commonly not enveloped by neuroglial cells.

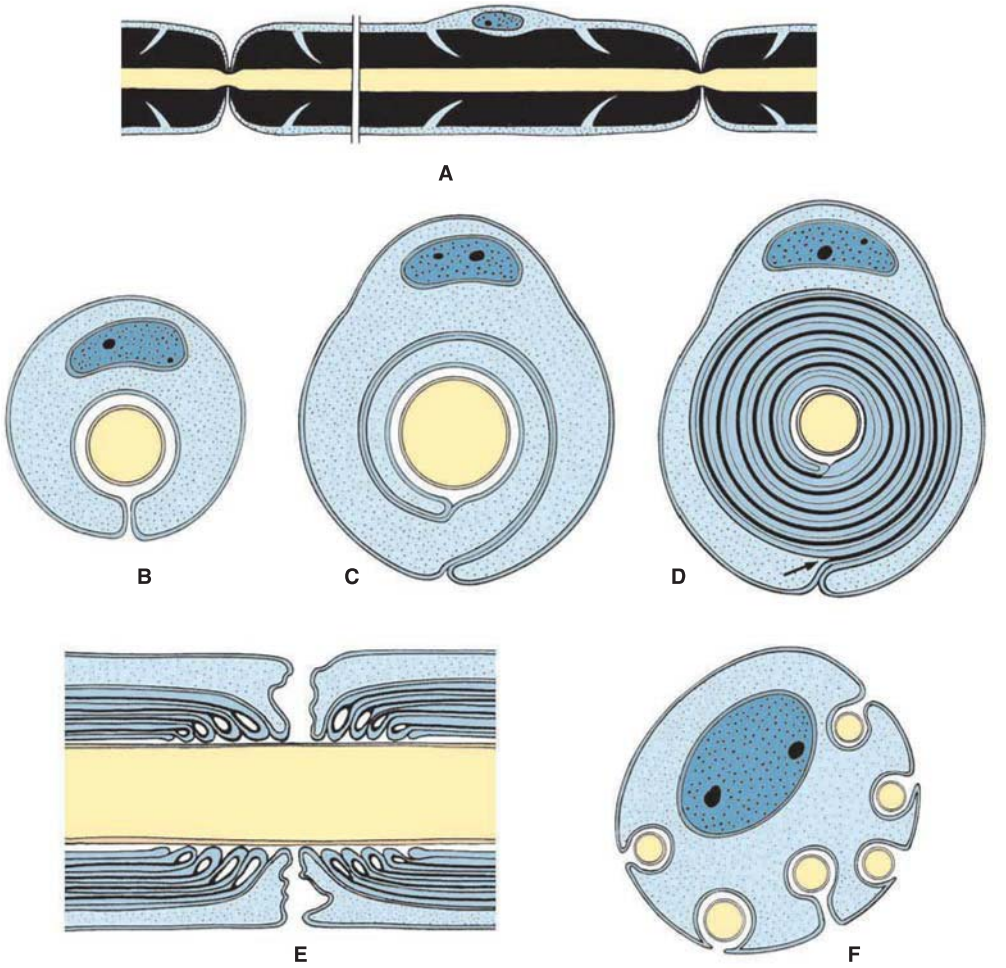


FIGURE 8.6. Myelin sheath formation. (**A**) Myelin sheath and the Schwann cell as they are seen (ideally) by light microscopy. (**B**, **C**, **D**) Successive stages in the development of the myelin sheath from plasma membrane of the Schwann cell. (**E**) Ultrastructure of a node of Ranvier, sectioned longitudinally. (**F**) Relation of the Schwann cell to several unmyelinated axons. (Reprinted with permission from Kiernan JA. *Barr's The Human Nervous System: An Anatomical Viewpoint*. 8th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2005:22.)

IV. SYNAPSES

Synapses are sites of **functional apposition** where signals are transmitted from one neuron to another or from a neuron to another type of cell (e.g., muscle cell, parenchymal cell of a gland).

A. Classification. Synapses are classified according to the site of synaptic contact and the method of signal transmission (Fig. 8.3).

1. **Site of synaptic contact. Axodendritic synapses** are located between an axon and a dendrite; **axosomatic synapses** are located between an axon and a soma (synapses in the CNS are primarily axodendritic and axosomatic); **axoaxonic synapses** are located between axons; and **dendrodendritic synapses** are located between dendrites.
2. **Method of signal transmission**
   a. **Chemical synapses**
      (1) Chemical synapses are the most common neuron–neuron synapse and the only neuron–muscle synapse. These synapses involve the release of a chemical substance, **neurotransmitter** or **neuromodulator** (**neurohormones**) by the presynaptic cell, which acts on the postsynaptic cell to generate an action potential. Neurotransmitters act directly on ion channels of the postsynaptic membrane whereas neuromodulators utilize a second messenger system to evoke a response in the postsynaptic cell. Therefore, neurotransmitters evoke a faster response than neuromodulators. Because they both have the same function, in this book, they are referred to as neurotransmitters.
      (2) Signal transmission across these synapses is **delayed** by about 0.5 ms, the time required for secretion and diffusion of neurotransmitter from the presynaptic membrane of the first cell into the synaptic cleft and then to the postsynaptic membrane of the receiving cell.

CLINICAL CONSIDERATIONS

Parkinson disease is a progressive degenerative disease that affects in excess of 8 million people in the world and is characterized by tremors, muscular rigidity, slow voluntary shuffling movement, difficulty in initiating movements, impaired balance, alterations in speech and writing, and a masklike facial expression. The cause appears to be the loss of dopaminergic neurons from the substantia nigra of the brain. Certain industrial toxins, such as those to which manganese miners are exposed, and the poisonous MTPT (methyl-phenyl-tetrahydropyridine), a substance present in illegally manufactured heroin, cause Parkinson disease. Neuropathologic findings in patients who died of Parkinson disease have demonstrated the presence of **Lewy bodies**, composed mostly of **α-synuclein** and other proteins, such as **Tau proteins**, **neurofilaments protein**, and **ubiquitin**, in dopaminergic neurons of the substantia nigra, suggesting that the presence of Lewy bodies is indicative of the disease. Recent studies may have determined the cause of death in dopaminergic neurons by demonstrating that Parkinson disease patients mount an immune response to α-synuclein, resulting in the killing of dopaminergic neurons containing this protein. Although a cure for Parkinson disease does not exist, early treatment modalities include oral administration of a blend of levodopa and carbidopa, which gives some relief, although the cells continue to die; once the disease progresses to a greater degree the levodopa–carbidopa may be administered as an infusion. Additional drugs, such as dopamine agonists, monoamine oxidase inhibitors, amantadine, and anticholinergics, that prolong and/or enhance the effects of levodopa–carbidopa may also be administered, provided that the patient can tolerate their side effects. The disease is difficult to diagnose, but if the patient responds to the levodopa–carbidopa complex, then the Parkinson disease diagnosis is most probably correct.

Because almost three quarters of Parkinson disease patients also suffer from constipation and/or other gastrointestinal problems, a correlation between the disease and the individual's intestinal flora has been suggested. Apparently, at least in mice, certain intestinal bacteria produce the protein α-synuclein, which is transferred to the brain via the vagus nerve (CN X). Once in the brain, the α-synuclein is stored by astrocytes of the substantia nigra, which transfer the protein to dopaminergic neurons and the infected neurons are killed in the immune response. Controlling the immune response is hoped to offer a cure for this disease. Another avenue to help control advanced cases of Parkinson disease, especially if the patient does not respond to medication or is unable to cope with their side effects, is a surgical intervention known as **deep brain stimulation.** This involves implanting electrodes into the patient's brain and using a battery-powered neurostimulator placed beneath the skin to generate electrical impulses to block the brain's electrical signals that produce the symptoms of Parkinson disease.

b. Electrical synapses

(1) These synapses involve movement of ions from one neuron to another via **gap junctions**, which transmit the action potential of the presynaptic cell directly to the postsynaptic cell.

(2) Electrical synapses are much less numerous than chemical synapses.

(3) Signal transmission across these synapses is **nearly instantaneous**.

B. Synaptic morphology

1. **Axon terminals** may vary morphologically depending on the site of synaptic contact.
   a. **Boutons terminaux** are bulbous expansions that occur singly at the end of axon terminals.
   b. **Boutons en passage** are swellings along the axon terminal; synapses may occur at each swelling.
2. The **presynaptic membrane** is the thickened axolemma of the neuron that is transmitting the impulse. It contains **voltage-gated Ca^{2+}** channels, which regulate the entry of calcium ions into the axon terminal. In response, synaptic vesicles fuse with and become incorporated into the presynaptic membrane before releasing their neurotransmitter substances.
3. The **postsynaptic membrane** is the thickened plasma membrane of the neuron or other target cell that is receiving the impulse.
4. The **synaptic cleft** is the narrow space (20–30 nm wide) between the presynaptic and postsynaptic membranes. Neurotransmitters diffuse across the synaptic cleft.
5. **Synaptic vesicles** are small, membrane-bound structures (40–60 nm in diameter) in the axoplasm of the transmitting neuron. They move to the **active sites** of the presynaptic membrane, fuse with it, and **discharge their neurotransmitters** into the synaptic cleft by exocytosis. **Cell adhesion molecules** facilitate the movement of the synaptic vesicles to and their fusion with the active sites of the presynaptic membrane (Table 8.2). Fusion of the synaptic vesicles results in an enlarged presynaptic membrane but the recapture of the extra membrane is performed by **clathrin-mediated endocytosis**.

C. Neurotransmitters and neuromodulators (Table 8.3) are produced, stored, and released by presynaptic neurons.

They diffuse across the synaptic cleft and bind to receptors in the postsynaptic membrane, leading to generation of an action potential. **Neurotransmitters** are subdivided into four types:

1. **Small molecule transmitters** (***acetylcholine***; ***amino acids:*** glutamate, aspartate, glycine, and γ-aminobutyric acid (GABA); ***biogenic amines:*** serotonin—and the three *catecholamines:* dopamine, norepinephrine, and epinephrine)
2. **Neuropeptides** (***opioid peptides:*** enkephalins and endorphins; ***gastrointestinal peptides:*** substance P, neurotensin, and vasoactive intestinal peptide [VIP]; ***hypothalamic releasing hormones:*** thyrotropin, somatostatin; ***neurohypophyseal hormones:*** antidiuretic hormone, oxytocin)
3. **Gases** (nitric oxide [NO] and carbon monoxide [CO])
4. **Other** (ATP and adenosine)

table **8.2** Principal Molecules of Synaptic Vesicles and Their Function

Molecule	Function
Synaptin-I	Maintains synaptic vesicles in a cluster away from active site
Synapsin-II and rab3a	Control connection of synaptic vesicles with actin filaments
Synaptotagmin and synaptophysin	Facilitate docking of synaptic vesicle to active site
SNARE protein complex (SNAP receptor)	Under the influence of Ca^{2+} ions permits the fusion of the synaptic vesicles with the postsynaptic membrane and the release of their contents into the synaptic cleft. It is composed of four α-helices: synaptobrevin, syntaxin, and two SNAP-25
Synaptobrevin	One of the SNARE proteins that organizes the SNARE protein complex
Syntaxin	One of the SNARE proteins that facilitates synaptic vesicle fusion with the active site
SNAP-25	One of the SNARE proteins; binds synaptobrevin and syntaxin enhancing synaptic vesicle docking and exocytosis

table 8.3 Common Neurotransmitters

Neurotransmitter	Type	Major Function	Location	Miscellaneous
Acetylcholine	Small molecule	Excitatory/ inhibitory	Myoneural junction; autonomic nervous system	Removed by the enzyme acetylcholinesterase; cholinergic neurons degenerate in Alzheimer disease
Adenosine triphosphate	Other	Excitatory	Motoneurons of the spinal cord; autonomic ganglia	Also co-released with numerous neurotransmitters
Dopamine	Small molecule	Excitatory	Neurons of the central nervous system (CNS)	Associated with Parkinson disease; inhibition of prolactin release; schizophrenia
Dynorphin	Neuropeptide	Inhibitory	Neurons of the CNS	Functions in pain suppression
Endorphin	Neuropeptide	Inhibitory	Neurons of the CNS	Functions in pain suppression
Enkephalin	Neuropeptide	Inhibitory	Neurons of the CNS	Functions in pain suppression
γ-Aminobutyric acid (GABA)	Small molecule	Inhibitory	Interneurons of the CNS	GABA synthesis is decreased in vitamin B_6 deficiency
Glutamate	Small molecule	Excitatory	Most excitatory neurons of the CNS	Astrocytes and neurons interact via the glutamate–glutamine cycle to ensure a supply of glutamate
Glycine	Small molecule	Inhibitory	Neurons of the brainstem and spinal cord	Strychnine acts to block the activity of glycine
Nitric oxide	Gas	Inhibitory	Neurons of the CNS	Smooth muscle relaxant, thus strong vasodilator
Norepinephrine (noradrenaline)	Small molecule	Excitatory	Postganglionic sympathetic neurons	Associated with depression, anxiety, and panic
Serotonin	Small molecule	Excitatory	Pineal body, neurons of the spinal cord and midbrain	Associated with sleep modulation; arousal, cognitive behaviors
Somatostatin	Neuropeptide	Inhibitory	Dorsal root ganglion cells and some neurons of the CNS	Also known as somatotropin release–inhibiting factor
Substance P	Neuropeptide	Excitatory	Dorsal root ganglia and trigeminal nerve ganglia	Associated with pain transmission
Vasoactive intestinal peptide	Neuropeptide	Excitatory and inhibitory	Diffuse neuroendocrine system and certain neurons of the CNS	GI tract: smooth muscle relaxant; induces water secretion; inhibits gastric HCl secretion Pituitary: stimulates prolactin secretion

CLINICAL CONSIDERATIONS

Huntington disease (**Huntington chorea**) is a fatal hereditary disease that becomes evident during the third and fourth decades of life, first presenting as painful joints and progressing to uncontrolled flicking of joints, motor dysfunction, dementia, and death. The cause is thought to be the loss of neurons that produce the neurotransmitter GABA. The symptoms of dementia are thought to be related to the loss of the cells secreting acetylcholine.

V. NERVE FIBERS

Nerve fibers are individual axons enveloped by a myelin sheath, Schwann cells in the PNS, or oligodendrocytes in the CNS.

A. Myelin sheath (Figs. 8.6 and 8.7)

1. The myelin sheath, produced by **oligodendrocytes** in the CNS and by **Schwann cells** in the PNS, consists of several spiral layers of the plasma membrane of an oligodendrocyte (or Schwann cell) wrapping around the axon. When stained with **osmium tetroxide** the myelin sheath stains black.

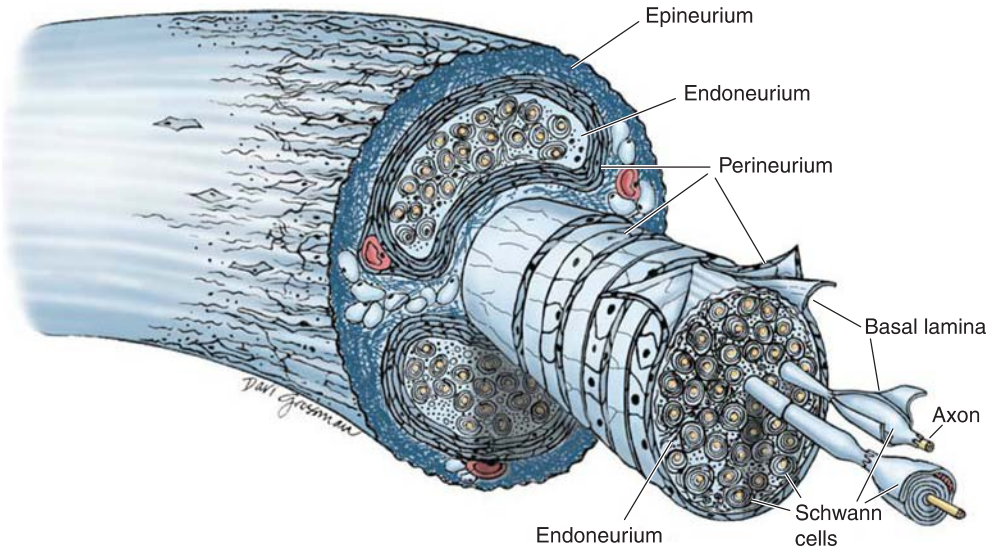


FIGURE 8.7. A peripheral nerve in cross-section showing the various connective tissue sheaths. Each bundle of nerve fibers, or fascicle (one is extended in drawing), is covered by perineurium. (Reprinted with permission from Kelly DE, Wood RL, Enders AC. *Bailey's Textbook of Microscopic Anatomy*. 18th ed. Baltimore, MD: Williams & Wilkins; 1984:353.)

2. It is not continuous along the length of the axon but is interrupted by gaps called **nodes of Ranvier** (Fig. 8.6E), but its thickness is constant along the length of an axon; however, thickness usually increases as axonal diameter increases.
3. Viewed with electron microscopy, the myelin sheath displays the following features:
   a. **Major dense lines** represent **fusions** between the cytoplasmic surfaces of the plasma membranes of Schwann cells (or oligodendrocytes).
   b. **Intraperiod lines** represent **close contact**, but not fusion, of the extracellular surfaces of adjacent Schwann cell (or oligodendrocyte) plasma membranes.
   c. **Clefts (incisures) of Schmidt–Lanterman** (observed in both electron and light microscopy) are cone-shaped oblique **discontinuities** of the myelin sheath because of the presence of Schwann cell (or oligodendrocyte) cytoplasm within the myelin.

B. Nodes of Ranvier **are regions along the axon that *lack myelin* and represent discontinuities between adjacent Schwann cells (or adjacent oligodendrocytes); *internodes* are the segments of a nerve fiber *between adjacent nodes of Ranvier*.**
1. In the PNS, the axon at the nodes of Ranvier is covered by interdigitated cytoplasmic processes of adjacent Schwann cells that protect the myelin-free surface of the axon. In the CNS, however, the axon is not covered by cytoplasmic processes of oligodendrocytes. Instead, the myelin-free surface of the axon at the node of Ranvier is covered by a foot plate of an astrocyte.
2. The axolemma at the nodes of Ranvier contains **many Na^+** pumps, and in electron micrographs, it displays a characteristic electron density.

C. The internodes **vary in length from 0.08 to 1 mm, depending on the size of the Schwann cells (or oligodendrocytes) associated with the fiber.** The axolemma of internodes contains **almost no Na^+** pumps; therefore, membrane depolarizations do not occur at the internodes.

CLINICAL CONSIDERATIONS

Multiple sclerosis (MS) is an immune-mediated disease characterized by chronic and progressive dysfunction of the nervous system caused by demyelination of the CNS, especially in the brain, spinal cord, and optic nerves. MS afflicts approximately 2.3 million people throughout the world and about 1 in 700 in the United States, most commonly affecting the 20- to 40-year age group, with a ratio of two females to one male. Random

episodes of inflammation, edema, and demyelination of axons occur followed by periods of remission that may last for months to years. Each episode may reduce the vitality of the patient and be sufficient to cause death within months. In the CNS, T lymphocytes mount an attack on myelin sheaths, demyelinate axons, and interfere with normal propagation of action potentials. However, recent studies have suggested that the true causative factor of MS is oligodendrogliopathy, and the T-cell response is merely a secondary reaction. Current treatments include immunosuppression with corticosteroids. The most severe form of the disease, known as primary progressive MS, afflicts about 350,000 people worldwide and causes severe disability, paralysis, and, frequently, sudden death. A recently approved drug, ocrelizumab (a monoclonal antibody against CD20), although quite expensive, kills B lymphocytes, thereby preventing them from presenting autoantigens to T lymphocytes. Because the T lymphocytes do not become activated, they do not migrate into the CNS to destroy the myelin sheath, which, otherwise, exacerbates the oligodendrogliopathy.

VI. NERVES

Nerves are cordlike bundles of nerve fibers surrounded by connective tissue sheaths (Fig. 8.7). They are **visible to the unaided eye** and usually appear **whitish** because of the presence of myelin.

A. Connective tissue investments

1. **Epineurium** is the layer of dense fibrous connective tissue (**fascia**) that forms the external coat of nerve bundles and is often embedded in adipose tissue.
2. **Perineurium** surrounds each bundle of nerve fibers (**fascicle**). Its inner surface consists of layers of flattened cells joined by **tight junctions** (zonulae occludentes) that prohibit passage of most macromolecules, thus assisting in the formation of the blood–nerve barrier (Fig. 8.8).

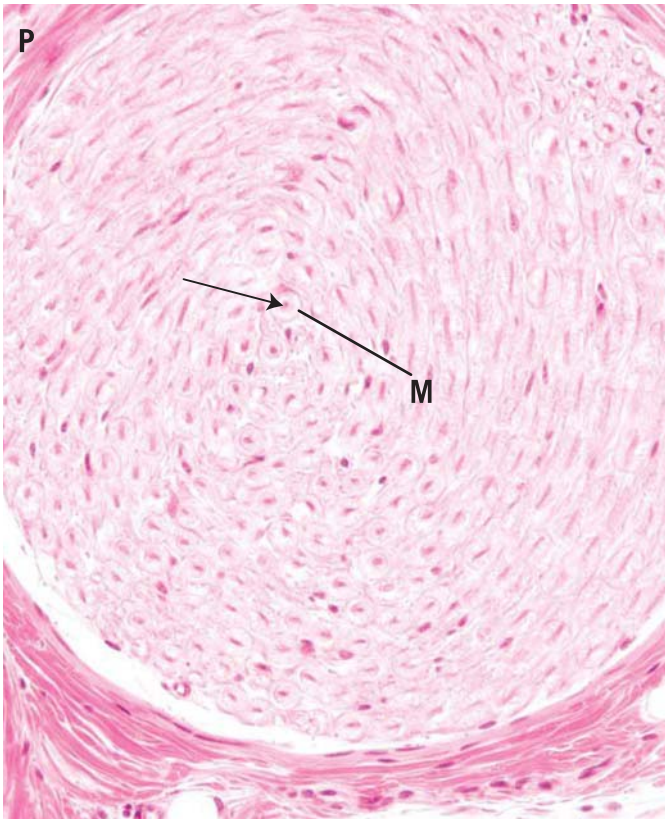


FIGURE 8.8. Light micrograph of peripheral nerve in cross-section (×132). Note that an axon (*tip of arrow*) is located in the center of the myelin sheath (M). P, perineurium.

table 8.4 Conduction Velocity of Nerve Fibers

Fiber Type and Function	Diameter (μm)	Fiber Velocity (m/s)
Type C: unmyelinated; chronic pain; postganglionic autonomic	0.5–1.5	0.5–2
Type B: somewhat myelinated; preganglionic autonomic; sensory	1–3	3–15
Type A: heavily myelinated; motor, proprioceptive, temperature, touch, and pressure; acute pain	1–20	15–120

3. **Endoneurium** is a thin layer of reticular fibers, produced mainly by Schwann cells, that surrounds individual nerve fibers. This layer, difficult to observe without specialized stains, contains occasional mast cells and macrophages.

B. Functional classification of nerves

1. **Sensory nerves** contain **afferent** fibers and carry sensory signals only from the internal and external environments to the CNS.
2. **Motor nerves** contain **efferent** fibers and carry signals only from the CNS to effector organs.
3. **Mixed nerves** are the most common type of nerve, containing both afferent and efferent fibers and thus carry both sensory and motor signals.

C. Conduction velocity of nerves.

The conduction velocity of nerve fibers depends greatly on their degree of myelination (Table 8.4). Those nerve fibers that are not myelinated have the slowest conduction velocity, whereas those that are heavily myelinated have the fastest conduction velocity.

VII. GANGLIA

Ganglia are encapsulated aggregations of **neuronal cell bodies** (**soma**) outside the CNS.

A. Autonomic ganglia

are *motor* ganglia in which axons of preganglionic neurons synapse on postganglionic neurons (see Section IX B).

B. Craniospinal ganglia

(Fig. 8.9) are *sensory* ganglia associated with most cranial nerves and the dorsal roots of spinal nerves (*dorsal root ganglia*). Unlike autonomic ganglia, craniospinal ganglia **do not possess synapses**. These ganglia contain the cell bodies of sensory neurons, which are **pseudounipolar** (**unipolar**) and transmit sensory signals from receptors to the CNS.

VIII. NERVOUS SYSTEM HISTOPHYSIOLOGY

A. Resting membrane potential

The resting membrane potential exists across the plasma membrane of all cells, including those of a neuron whose resting potential is negative, −70 mV inside the cell compared to outside the cell. This potential difference is established and maintained mostly by K^+ leak channels and to a much lesser extent by the **Na^+-K^+ pump**, which actively transports three Na^+ ions out of the cell in exchange for two K^+ ions. The resting potential exists when there is no net movement of K^+ (i.e., when outward diffusion of K^+ is just balanced by the external positive charge acting against further diffusion).

B. An action potential

is the electrical activity that occurs in a neuron as an impulse is propagated along its axon and is observed as a *movement of negative charges along the outside of an axon*. It is an **all-or-none event with a constant amplitude and duration.**

1. **Action potential generation**

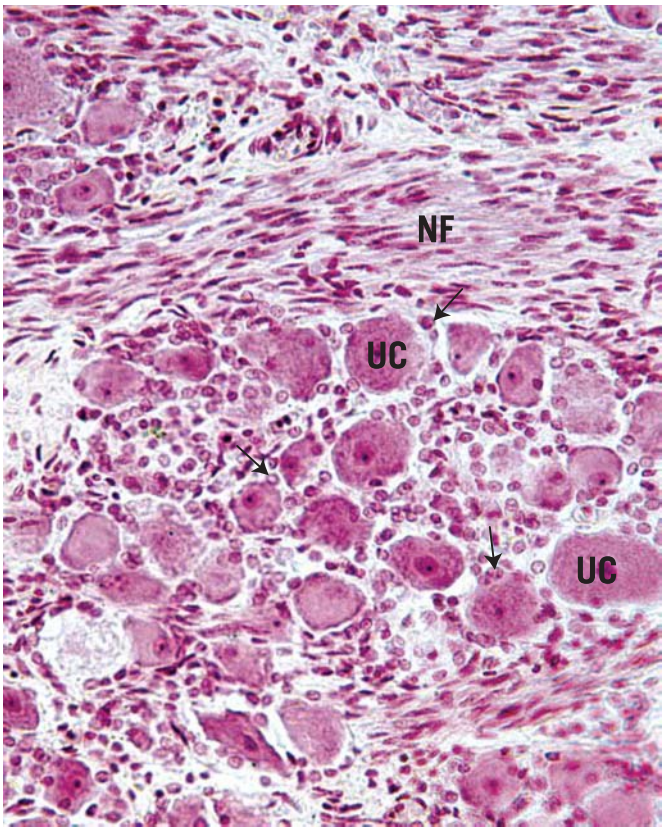


FIGURE 8.9. Light micrograph of a dorsal root ganglion displaying numerous unipolar (pseudounipolar) neuron cell bodies (UC) surrounded by satellite cells (*arrows*). The procentral and peripheral processes of these unipolar neurons are collected into bundles of nerve fibers (NF).

a. An excitatory stimulus on a postsynaptic neuron partially **depolarizes** a portion of the plasma membrane (the potential difference is **less negative**).
b. Once the membrane potential reaches a critical **threshold**, **voltage-gated Na^+ channels** in the membrane open, permitting Na^+ to enter the cell (Fig. 8.10).

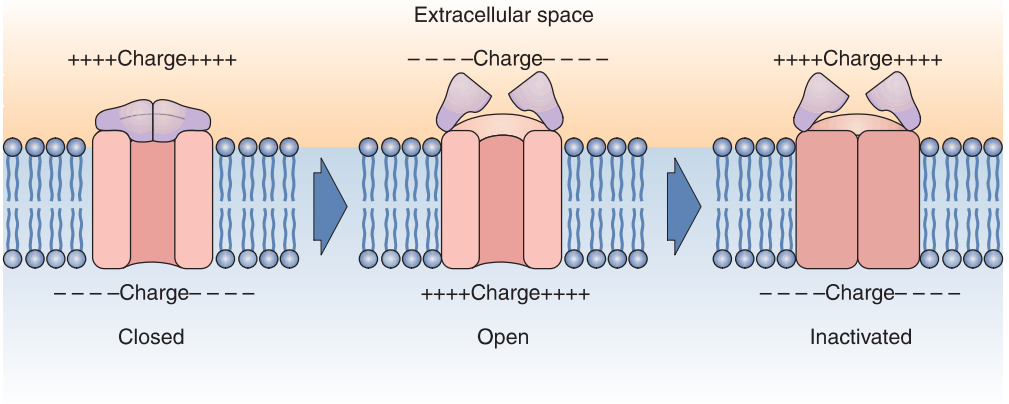


FIGURE 8.10. Model of the voltage-gated Na^+ channel showing the transition between its closed, open, and inactivated states. In the resting state, the channel-blocking segment and gating keep the channel closed to entry of extracellular Na^+. Depolarization of the membrane causes a conformational change that opens the channel to influx of Na^+. The channel closes spontaneously and becomes inactive within a millisecond after opening.

c. The influx of Na^+ leads to **reversal of the resting potential** in the immediate area (i.e., the external side becomes negative compared to the internal aspect), resulting in the spontaneous closure of the Na^+ channels, which become inactivated for 1 to 2 ms (**refractory period**).

d. Depolarization also triggers the opening of **voltage-gated K^+ channels**. Because these channels remain open longer than the Na^+ channels, exit of K^+ during the refractory period **repolarizes** the membrane to its resting potential and the ion channels then return to their normal states. The cell is now ready to respond to another stimulus.

2. **Action potential propagation**

a. Propagation of the action potential results from longitudinal diffusion of Na^+ (which enters the cell at the initial site of excitation) toward the axon terminals (**orthodromic spread**). The longitudinal diffusion of Na^+ depolarizes the adjacent region of membrane, giving rise to a new action potential at this site.

b. Propagation does **not** result from diffusion of Na^+ toward the soma (**antidromic spread**), because the Na^+ channels are in their **refractory period** in this region.

c. Action potentials are propagated most rapidly in myelinated fibers, which exhibit **saltatory conduction**. In this type of conduction, the action potential jumps from one node of Ranvier to the next because Na^+ channels are restricted to these nodes.

C. Axons transport **proteins, organelles, and vesicles along their axoplasm in both directions at different velocities, depending on the nature of the transported materials.** This transport is known as **axonal transport** (Table 8.5).

1. **Anterograde transport** carries material away from the soma.
2. **Retrograde transport** carries material toward the soma for reuse, recycling, or degradation. However, some viruses (e.g., herpes simplex and rabies) spread in this manner. Also, some toxins (e.g., tetanus) move from the periphery to the CNS in this manner.

D. Trophic function of nervous tissue

1. **Denervation** of a muscle or gland leads to its atrophy.
2. **Reinnervation** of a muscle or gland restores its structure and function.

IX. SOMATIC AND AUTONOMIC NERVOUS SYSTEMS

Somatic and autonomic are functional concepts relating to all the neural elements involved in transmission of impulses from the CNS to the somatic and visceral components of the body, respectively. Neural crest cells give rise to neurons of the parasympathetic and sympathetic divisions of the ANS whose preganglionic cell bodies are located in the CNS and **postganglionic cell bodies** are located in **autonomic ganglia** located outside the CNS.

A. The **SNS** contains sensory fibers that bring information to the CNS and the motor fibers that originate in the CNS that innervate voluntary **skeletal muscles**.

B. The **ANS** is generally considered to be purely motor in function because it contains motor fibers that control and regulate **smooth muscle**, **cardiac muscle**, and some **glands**. It establishes and maintains

table 8.5 Types of Axonal Transport

Type of Transport	Transport Velocity (mm/day)	Transported Material
Retrograde (fast)	200–300	Proteins, enzymes, lysosomes
Anterograde (fast)	50–500	Mitochondria, vesicles, secretory granules
Anterograde (slow)	1.0–10	Clathrin, actin, myosin, enzymes, proteins
Anterograde (very slow)	0.1–1.0	MAPs, tubulin, neurofilaments proteins

MAPs, microtubule-associated proteins.

homeostasis of the body's visceral functions. Anatomically and functionally, the ANS is divided into three parts: the **sympathetic**, **parasympathetic**, and **enteric nervous systems**. The sympathetic and parasympathetic nervous systems generally **function antagonistically** in a given organ (i.e., when the sympathetic system stimulates an organ, the parasympathetic inhibits it, and vice versa). The enteric nervous system is confined to the digestive system where it controls digestive processes; however, it is modulated by the sympathetic and parasympathetic nervous systems.

1. **Autonomic nerve chains**
   a. Cell bodies of **preganglionic neurons** are located in the CNS and extend their **preganglionic fibers** (axons) to an **autonomic ganglion** located outside of the CNS.
   b. In the ganglion, the preganglionic fibers synapse with postganglionic neurons, which typically are multipolar and surrounded by satellite cells.
   c. **Postganglionic fibers** leave the ganglion and terminate in the **effector organ** (smooth muscle, cardiac muscle, and glands).
2. **Sympathetic system** (**thoracolumbar outflow**)
   a. Preganglionic cell bodies of the sympathetic nervous system are located in the thoracic and the first two lumbar segments of the spinal cord.
   b. **Function.** The sympathetic system effects **vasoconstriction**. In general, it functions to prepare the body for **flight-or-fight-or-freeze** (freeze in extreme cases) responses by increasing heart rate, respiration, blood pressure, and blood flow to skeletal muscles; dilating pupils; and decreasing visceral function. In extreme cases, mostly to escape predators, the individual "freezes," that is, faints (resulting in reduced respiration and heart rate) and appears to be dead.
3. **Parasympathetic system** (**craniosacral outflow**)
   a. Preganglionic cell bodies of the parasympathetic nervous system are located in certain cranial nerve nuclei within the brain and in some sacral segments of the spinal cord.
   b. **Function.** The parasympathetic system stimulates secretion (**secretomotor** function). In general, it functions to prepare the body for rest-or-digest functions by decreasing heart rate, respiration, and blood pressure; constricting pupils; and increasing visceral function.
4. **Enteric nervous system**
   a. Consists of two divisions of neurons located in the wall of the digestive tract: the **myenteric plexus of Auerbach** and the **submucosal plexus of Meissner**.
   b. **Function.** The enteric system is a stand-alone system that is generally responsible for the proper course of digestion including the control of digestive secretions and blood flow to and from the gut. Although the enteric system is considered to be an independent system, its functions are modulated by the sympathetic and parasympathetic components of the ANS.

X. CENTRAL NERVOUS SYSTEM

The **CNS** consists of the brain, housed in the skull, and the spinal cord located in the bony vertebral column.

A. White matter and gray matter are both present in the CNS.

1. **White matter** contains mostly myelinated nerve fibers but also some unmyelinated fibers and neuroglial cells, whereas **gray matter** contains neuronal cell bodies, many unmyelinated fibers, some myelinated fibers, and neuroglial cells.
2. **Spinal cord gray matter** appears in the shape of an H in cross-sections of the spinal cord (Fig. 8.11).
   a. A small **central canal**, lined by ependymal cells, is at the center of the crossbar in the H. This canal is a remnant of the embryonic neural canal.
   b. The dorsal vertical bars of the H (**dorsal horns**) consist of **sensory** fibers extending from the dorsal root ganglia and cell bodies of interneurons.
   c. The ventral vertical bars of the H (**ventral horns**) consist of cell bodies and fibers of large multipolar motor neurons.
3. **Brain gray matter** is located at the periphery (cortex) of the cerebrum and cerebellum. White matter lies beneath the gray matter in these structures.

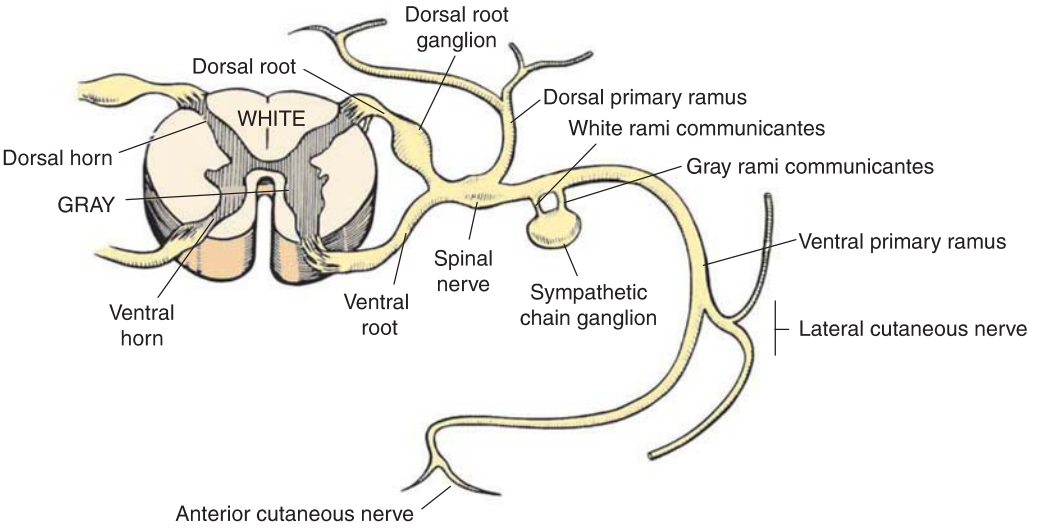


FIGURE 8.11. Typical thoracic spinal cord segment with spinal nerve. (Reprinted with permission from Hiatt JL, Gartner LP. *Textbook of Head and Neck Anatomy*. 4th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2010:25.)

a. The **Purkinje cell layer** (***cerebellar cortex only***) consists of flask-shaped Purkinje cells. These cells have a central nucleus, highly branched (arborized) dendrites, and a single myelinated axon. These cells may receive several hundred thousand excitatory and inhibitory impulses to sort and integrate (Figs. 8.2 and 8.12).

b. Brain gray matter also forms the **basal nucleus** (**basal ganglia**) **and other nuclei**, which are surrounded by white matter.

B. Meninges, formed from connective tissue, are *membranous coverings of the brain and spinal cord.* The three layers of meninges are the outermost **dura mater**; lining the bony skull and spinal cord, the intermediate **arachnoid mater**; abutting the dura, and the innermost, the highly vascular **pia mater** lying directly on the surface of the brain and spinal cord.

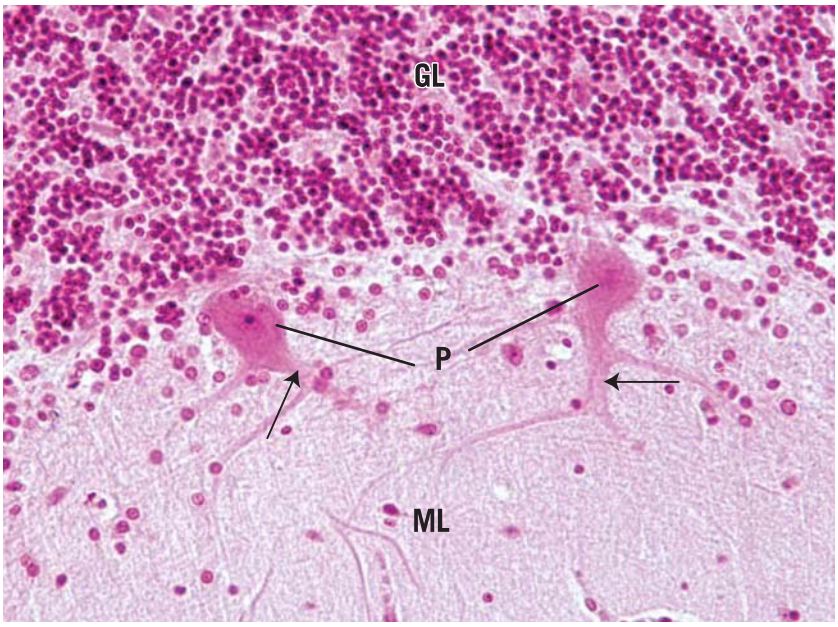


FIGURE 8.12. Light micrograph of the cerebellum (×132). Observe the Purkinje cells (P) with their dendritic trees (*arrows*) protruding into the molecular layer (ML). The heavily populated and deeply stained region is the granular layer (GL) of the cerebellum.

CLINICAL CONSIDERATIONS

Meningitis results from an inflammation of the meninges caused by viral or bacterial infection of the CSF. Viral meningitis is not severe, but bacterial meningitis is contagious and dangerous, leading to hearing loss, learning disability, brain damage, and death, sometimes within 24 hours if untreated. In the United States, children 4 years of age or younger have been vaccinated for the most prevalent form of the bacterium. Recently, because of so many outbreaks of meningitis on college campuses, several schools have chosen to vaccinate all students and those in close contact with them. Major symptoms include fever, headache, stiff neck, and alteration of consciousness with rapid onset and progression. Spinal tap and culture of CSF to determine the bacterial species is the only diagnosis. This is followed by treatment with a specific antibiotic. Bacterial meningitis can be spread by respiratory and throat secretions (i.e., coughing, sneezing, kissing).

C. Cerebrospinal fluid

1. CSF a clear fluid, composed of 90% water and ions and contains little protein, occasional white blood cells, and infrequent desquamated cells, is produced primarily by cells of the **choroid plexus** in the ventricles of the brain. The choroid plexus is composed of folds of pia mater and capillaries that are surrounded by cuboidal ependymal cells.
2. CSF circulates through the ventricles, subarachnoid space, and central canal, bathing and nourishing the brain and spinal cord; it also acts as a shock-absorbing cushion to protect these structures.
3. CSF is continuously produced; it is reabsorbed by **arachnoid granulations** that transport it into the superior sagittal sinus. If reabsorption is blocked, **hydrocephalus** may occur.
4. The **blood–brain barrier** functions to isolate the nervous tissue of the CNS from products carried by the blood vascular system. Tight junctions formed by adjacent endothelial cells lining the continuous capillaries supplying the neural tissues perform this function. Although this barrier permits the passage of certain molecules (i.e., O_2, H_2O, CO_2, lipids, and certain drugs), other substances such as vitamins, most drugs, and glucose are afforded access only via diffusion or receptor-mediated transport. Additionally, certain ions can also pass through the blood–brain barrier by the use of active transport. Protoplasmic astrocytes assist in the maintenance of the blood–brain barrier.

CLINICAL CONSIDERATIONS

A small amount of CSF can be extracted safely for analysis by **lumbar puncture**, which involves inserting a needle into vertebral canal between the third and fourth lumbar vertebrae, which, in most adults, is below the terminal end of the spinal cord.

The integrity of the **blood–brain barrier** prevents many substances, including some neurotransmitters and drugs, from penetrating it. In order to permit the delivery of certain drugs through the blood–brain barrier, procedures were developed such as perfusion with a hypertonic solution, **mannitol**. This polyhydric alcohol temporarily disables the fasciae occludentes of the capillary endothelial cells, allowing the delivery of certain therapeutic drugs.

XI. NERVE TISSUE DEGENERATION AND REGENERATION

A. Death of neurons occurs as the result of injury to or disease affecting the somata.

1. Neuronal death has been described until recently as resulting in degeneration and permanent loss of nerve tissue because it was believed that neurons of the CNS could not divide. However, recent evidence shows that neuronal stem cells within certain regions of the brain exhibit multipotential capability and can be stimulated to differentiate into glial cells and neurons, replacing those that were lost or injured in the damaged tissue.
2. In the CNS, neuronal death may be followed by proliferation of the neuroglia, which fills in areas left by dead neurons.

B. Transection of peripheral axons induces changes in the soma, including *chromatolysis* (disruption of Nissl bodies with a concomitant loss of cytoplasmic basophilia), increase in soma volume, and movement of the nucleus to a peripheral position.

1. **Degeneration of distal axonal segment** (anterograde changes). The axon and its myelin sheath, which are separated from the soma, degenerate completely (**Wallerian degeneration**) and the remnants are removed by macrophages. Schwann cells proliferate, forming a **solid cellular column** that is distal to the injury and that remains attached to the effector cell.
2. **Regeneration of proximal axonal segment** (retrograde changes) (Fig. 8.13)
   a. The distal end, closest to the wound, initially degenerates, and the remnants are removed by macrophages. Growth at the distal end then begins (0.5–3 mm/d) and progresses toward the columns of Schwann cells.
   b. Regeneration is successful if the sprouting axon penetrates a Schwann cell column and reestablishes contact with the effector cell.

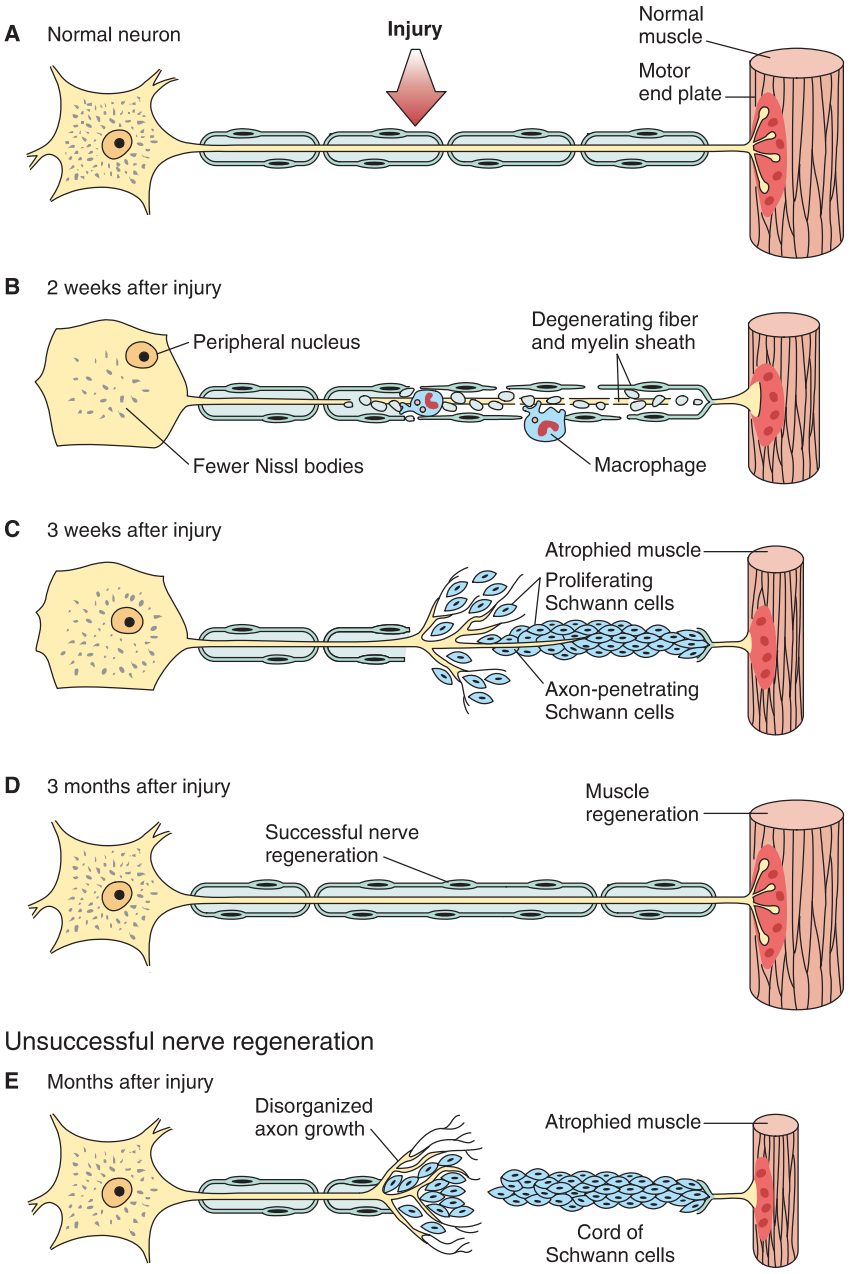


FIGURE 8.13. Peripheral nerve regeneration. (Adapted with permission from Gartner LP. *Textbook of Histology*. 4th ed. Philadelphia, PA: Elsevier; 2017.)

Review Test

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A patient with Hirschsprung disease is most likely to present with which of the following symptoms?

(A) Absent cranial vault
(B) Exposed spinal cord
(C) Headache
(D) Large, dilated colon
(E) Absent small intestine

2. Episodes of demyelination are associated with which of the following conditions?

(A) Meningitis
(B) Huntington chorea
(C) Spina bifida
(D) Parkinson disease
(E) Multiple sclerosis

3. Tremors, shuffling gate, and masklike facial expressions are associated with which of the following conditions?

(A) Meningitis
(B) Huntington chorea
(C) Spina bifida
(D) Parkinson disease
(E) Multiple sclerosis

4. Loss of the neurotransmitter GABA is associated with which of the following conditions?

(A) Meningitis
(B) Huntington chorea
(C) Spina bifida
(D) Parkinson disease
(E) Multiple sclerosis

5. Rapid onset of fever, stiff neck, headache, and an altered state of consciousness are associated with which of the following conditions?

(A) Meningitis
(B) Huntington chorea
(C) Spina bifida
(D) Parkinson disease
(E) Multiple sclerosis

6. Deterioration and death of the dopaminergic neurons within the substantia nigra of the brain are associated with which of the following conditions?

(A) Meningitis
(B) Huntington chorea
(C) Spina bifida
(D) Parkinson disease
(E) Multiple sclerosis

7. Which of the following neurotransmitters functions to increase cardiac output in patients?

(A) Dopamine
(B) Serotonin
(C) Norepinephrine
(D) Glutamate
(E) GABA

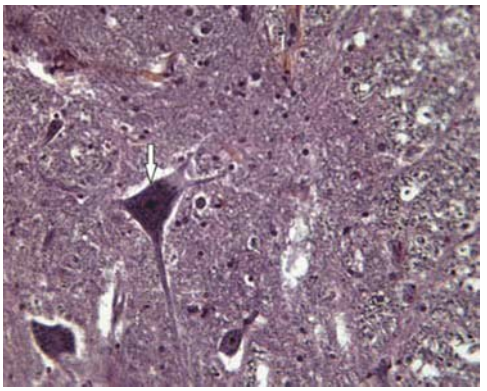
8. Acetylcholine is the only neurotransmitter in which of the following regions of the nervous system?

(A) CNS
(B) Presynaptic sensory cortex
(C) Myoneural junctions
(D) Postganglionic sympathetic synapses
(E) Motor cortex

9. A patient has to have a certain drug delivered to neurons in his brain that cannot cross the blood–brain barrier. In order to assist the drug in reaching its target cell the physician can inject a hypertonic solution of which polyhydric alcohol?

(A) Glycerol
(B) Mannitol
(C) Sorbitol
(D) Inositol
(E) Xylitol

Question 10 is based on the following photomicrograph:



10. The cell at the tip of the arrow is located in which of the following regions of the nervous system?

(A) Cerebellum
(B) Cerebrum
(C) Spinal cord
(D) Dorsal root ganglion
(E) Autonomic ganglion

Answers and Explanations

1. **D.** Hirschsprung disease is characterized by a dilated colon caused by the absence of the parasympathetic myenteric ganglia known as Auerbach plexus.
2. **E. MS** is an immune-mediated disease exhibiting chronic and progressive dysfunction of the nervous system caused by demyelination of the CNS and optic nerves, striking the 20- to 40-year age group affecting two times more women than men. Random episodes of inflammation, edema, and demyelination of axons occur, followed by periods of remission. Each episode may reduce the vitality of the patient and be sufficient to cause death within months.
3. **D.** Parkinson disease is a progressive degenerative disease characterized by tremors, muscular rigidity, difficulty in initiating movements, slow voluntary shuffling movement, and masklike face. The cause is the loss of dopaminergic neurons from the substantia nigra of the brain.
4. **B. Huntington chorea** is a fatal heredity disease that becomes evident during the third and fourth decades of life. It progresses to uncontrolled flicking of joints, motor dysfunction, dementia, and death. The cause is apparently the loss of neurons that produce the neurotransmitter GABA. Dementia symptoms are thought to be related to the loss of cells secreting acetylcholine.
5. **A. Meningitis** results from an inflammation of the meninges caused by viral or bacterial infection in the CSF. Although viral meningitis is not severe, bacterial meningitis is contagious and dangerous, leading to hearing loss, learning disability, brain damage, and death if untreated, sometimes within 24 hours. Major symptoms include fever, headache, stiff neck, and alteration of consciousness with rapid onset and progression. Spinal tap and culture of CSF to determine the bacterial species is the only diagnosis. Treatment is by species-specific antibiotic. Bacterial meningitis can be spread by respiratory and throat secretions (i.e., coughing, sneezing, kissing).
6. **D. Parkinson disease** is a progressive degenerative disease characterized by tremors, muscular rigidity, difficulty in initiating movements, slow voluntary shuffling movement, and masklike face. It is caused by the loss of dopaminergic neurons from the substantia nigra of the brain.
7. **C.** Norepinephrine increases cardiac output, whereas dopamine and γ-aminobutyric acid are CNS inhibitors. Glutamate is the most common excitatory neurotransmitter of the CNS. Serotonin functions as a pain inhibitor in mood control and in sleep.
8. **C.** Acetylcholine is the neurotransmitter for myoneural junctions as well as for preganglionic sympathetic and preganglionic and postganglionic parasympathetic synapses.
9. **B.** Of all the polyhydric alcohols (sugar alcohols) listed, only a hypertonic solution of mannitol has the ability to temporarily disable the fasciae occludentes of the capillary endothelial cells, allowing the delivery of certain therapeutic drugs to neurons of the CNS.
10. **C.** The cell at the tip of the arrow in the photomicrograph is a multipolar neuron (motoneuron) from the ventral horn of the spinal cord.

chapter 9

Circulatory System

I. OVERVIEW—BLOOD VASCULAR SYSTEM

The blood vascular system consists of the heart, arteries, veins, and capillaries. This system transports **oxygen** and **nutrients to tissues**, carries **carbon dioxide** and **waste products** from **the tissues**, and circulates **hormones** from the site of synthesis to their target cells.

A. Heart. The *heart*, a four-chambered pump composed of two atria and two ventricles, is surrounded by a fibroserous sac called the *pericardium*. Atria are receiving chambers, whereas ventricles are discharging chambers. Moreover, the heart is divided functionally into the right heart (pulmonary circuit) and the left heart (systemic circuit). The right atrium receives venous blood from the body and discharges it into the right ventricle. From here the blood is pumped into the pulmonary trunk to be distributed to the lungs. Venous blood from the pulmonary system is received in the left atrium and then discharged into the left ventricle to be pumped out through the aorta into the systemic circulation.

The heart receives **sympathetic innervation** via upper thoracic levels of the spinal cord (accelerating the heart rate, increasing the force of the heartbeat, and dilating the coronary vessels) and **parasympathetic innervation** via the vagus nerves (which slows the heart rate, reduces the force of the heartbeat, and constricts the coronary vessels). Muscle cells of the atria produce **atrial natriuretic peptide**, whereas muscle cells of the ventricles produce **B-type natriuretic peptide,** hormones that increase secretion of sodium and water by the kidneys, inhibit renin release, and decrease blood pressure.

CLINICAL CONSIDERATIONS

Tetralogy of Fallot, a **congenital malformation** frequently due to trisomy 21 as well as fetal alcohol syndrome, consists of four heart defects: a defective interventricular septum, hypertrophy of the right ventricle (because of a narrow pulmonary artery or valve), impediment of the outflow from the right ventricle, and transposed (dextroposed) aorta. Depending on the size of the defect in the interventricular septum, some or much of the blood may pass directly from the right ventricle to the left ventricle, bypassing oxygenation in the lung. Thus, the blood that leaves the left ventricle is poorly oxygenated. Common symptoms of tetralogy of Fallot include clubbed fingers and toes, retarded growth, cyanosis, shortness of breath (especially after physical exertion), and a strident heart murmur. The condition should be **repaired surgically** early in life, before the pulmonary constriction becomes exacerbated.

1. **The heart has three layers** (from internal to external): endocardium, myocardium, and epicardium.
   - **a.** The **endocardium** lines the lumen of the heart and is composed of simple squamous epithelium (**endothelium**) and a thin layer of loose connective tissue. An additional loose connective tissue layer, the subendocardial layer, that contains veins, nerves, and Purkinje fibers, underlies the endocardium.
   - **b.** The **myocardium** consists of numerous layers of **cardiac muscle cells** arranged in a spiral fashion about the heart's chambers and inserted into the fibrous skeleton of the heart, consisting

of thick bundles of **collagen fibers** oriented in various directions and especially oriented to support the valve rings of the heart valves. The myocardium contracts to propel blood into arteries for distribution to the body.

c. The **epicardium** (**visceral layer of the pericardium**) is the outermost layer of the heart. It is composed of simple squamous epithelium (**mesothelium**) on the external surface. Beneath the mesothelium lies fibroelastic connective tissue, containing nerves, the coronary vessels, and adipose tissue. The epicardium reflects upon itself at the roots of the major vessels of the heart to become continuous with the very smooth **serous** (**parietal**) **pericardium**. The space between these two layers is the **pericardial cavity**. The external layer of the serous pericardium is more fibrous and rougher in consistency and is known as the **fibrous pericardium**.

2. **Heart valves** control blood flow into and out of the heart.
   a. The **atrioventricular** (**AV**) valves are composed of a skeleton of fibrous connective tissue, arranged like an aponeurosis, and lined on both sides by endothelium and control blood flow from the atria into the ventricles. The AV valves are attached to the **annuli fibrosi** of the fibrous skeleton. The right AV valve is formed of three interlocking cusps (**tricuspid valve**), whereas the left AV valve is formed of two interlocking cusps (**bicuspid or mitral valve**). These valves prevent regurgitation of ventricular blood into the atria.
   b. Blood leaving the heart is controlled by the **semilunar valves**, located in the pulmonary and aortic trunks. Each semilunar valve is composed of three cusps that approximate each other as they fill with arterial blood. They are lined with endothelium on both sides separated by sparse strands of connective tissue. These valves prevent regurgitation of pulmonary and aortic blood into the respective ventricles.

CLINICAL CONSIDERATIONS

Rheumatic heart valve disease is a **sequela to childhood rheumatic fever** (subsequent to **group A β-hemolytic streptococcal infection**), which causes scarring of the heart valves, a condition that may have a familial component because there appears to be a genetic disposition that affects members of the same family. Fortunately, because of better health care for children in developed countries, the incidence of untreated childhood rheumatic fever has been greatly reduced. This involves immediate antibiotic regimen for children suffering from group A β-hemolytic streptococcal pharyngitis that may have to be continued for a long time. This rapid treatment modality is responsible for the reduction in the incidence of rheumatic heart valve disease, a condition that affects mostly the **mitral valve** and to a lesser extent the **aortic valve**. Both of the affected valves are characterized by their reduced elasticity, which makes them unable to close (**incompetence**) or open (**stenosis**) properly.

3. The **impulse-generating and impulse-conducting system** of the heart comprises several specialized structures, the sinoatrial (SA) node, the AV node, AV bundle of His, and Purkinje fibers, with coordinated functions that act to **initiate and regulate the heartbeat**. Additionally, the autonomic nervous system modulates the heart rate and stroke volume.
   a. The **SA node**, the **pacemaker** of the heart, is composed of specialized cardiac cells located within the wall of the right atrium adjacent to the entry of the superior vena cava into the heart. It **generates impulses** that initiate contraction of atrial muscle cells, which are then conducted to the AV node.
   b. The **AV node** is located in the wall of the right atrium, adjacent to the tricuspid valve.
   c. The **AV bundle of His** is a band of conducting tissue radiating from the AV node into the interventricular septum, where it divides into two branches and continues as **Purkinje fibers** (Fig. 9.1), large, modified cardiac muscle cells that make contact with cardiac muscle cells at the apex of the heart via gap junctions, desmosomes, and fasciae adherentes.

CLINICAL CONSIDERATIONS

Cardiac arrest occurs when the heart ceases to beat, resulting in cessation of blood flow in the entire circulatory system. Cardiac death is imminent unless cardiopulmonary resuscitation (CPR) and defibrillation are conducted successfully and the electrical system of the heart is revived. Health conditions that may lead to cardiac arrest include but are not limited to tachycardia, fibrillation, and bradycardia.

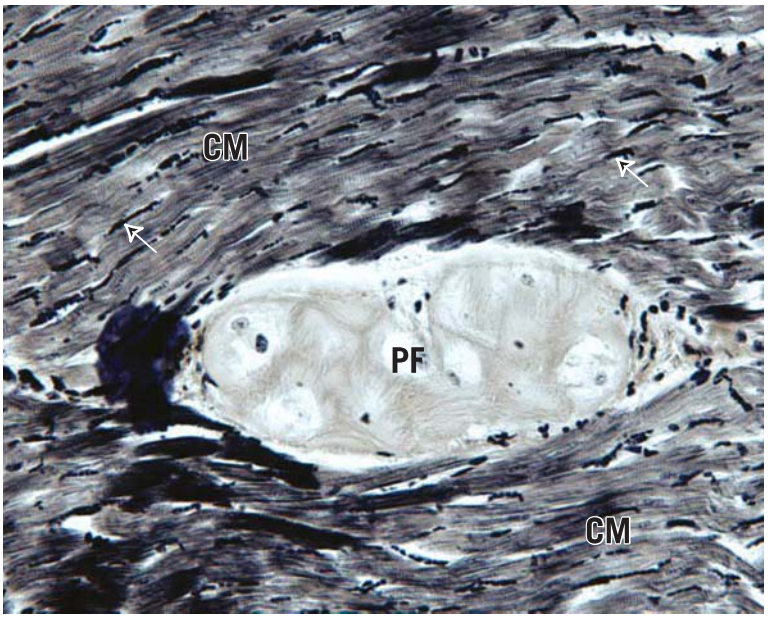


FIGURE 9.1. This is a light micrograph of Purkinje fibers (PF) embedded in cardiac muscle (CM). The *arrows* point to red blood cells in capillaries, attesting to the high degree of vascular supply of cardiac muscle. The light area separating the Purkinje fibers from the cardiac myocytes is occupied by slender elements of connective tissue.

B. Arteries conduct blood *away from the heart* to the organs and tissues. Arterial walls are composed of three layers (tunicae): the *tunica intima* (inner), *tunica media* (middle), and *tunica adventitia* (outer). The components of these layers and variations among types of arteries are summarized in Table 9.1. The four categories of arteries are elastic arteries, muscular arteries, arterioles, and metarterioles.

table 9.1 Comparison of Tunicae in Different Types of Arteries

Tunica Components	Elastic Arteries	Muscular Arteries	Arterioles	Metarterioles
Intima				
Endothelium	+	+	+	+
Factor VIII in endothelium	+	+	+	–
Basal lamina	+	+	+	+
Subendothelial layer*	+	+	±	–
Internal elastic lamina	Incomplete	Thick, complete	Some elastic fibers	–
Media				
Fenestrated elastic membranes	40–70	–	–	–
Smooth muscle cells	Interspersed between elastic membranes	≤40 layers	One or two layers	Discontinuous layer
External elastic lamina	Thin	Thick	–	–
Vasa vasorum	±	–	–	–
Adventitia				
Fibroblastic connective tissue	Thin layer	Thin layer	–	–
Loose connective tissue	–	–	+	±
Vasa vasorum	+	±	–	–
Lymphatic vessels	+	+	–	–
Nerve fibers	+	+	+	–

+, present and prominent; ±, present but not prominent; –, absent.
*In elastic arteries, the subendothelial layer is composed of loose connective tissue containing fibroblasts, collagen, and elastic fibers. In arterioles, this layer is less prominent; the connective tissue is sparse and contains a few reticular fibers.

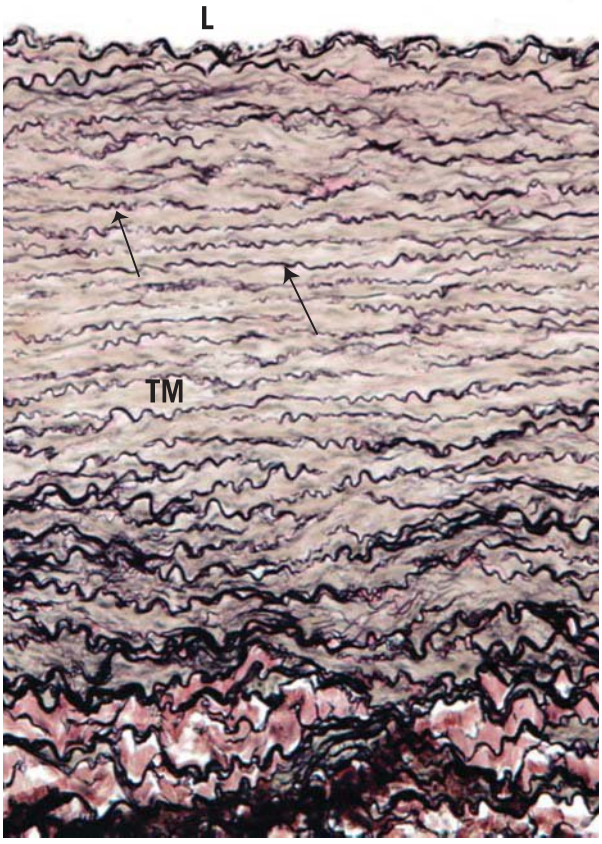


FIGURE 9.2. Light micrograph of the aorta (elastic stain) (×132). Observe the wavy elastic fibers (*arrows*) located in the tunica media (TM). Note the lumen (L) located at the top of the micrograph.

1. **Elastic arteries** (**conducting arteries**) are large vessels that include the **aorta** and its **major branches** (Figs. 9.2 and 9.3). These arteries help **reduce changes in blood pressure** associated with the heartbeat because of the thick concentric sheaths of **elastic membranes**, known as **fenestrated membranes**, located in the tunica media of these vessels. Small vessels (**vasa vasorum**) and nerves are present in the tunica adventitia and tunica media of these vessels, supplying them with vascularization and innervation.

CLINICAL CONSIDERATIONS

Atherosclerosis, the most common form of **arteriosclerosis**, is the most frequent cause of morbidity of the vascular diseases. It is characterized by deposits of yellowish plaques (**atheromas**) in the tunica intima of large and medium-sized arteries. The plaques may block blood flow to the region supplied by the affected artery. Continued deposits form plaques that reduce the lumina of the vessels, and the patient may feel referred pain and pressure. Sustained narrowing results in complete blockage and ischemia of the tissues, which may be fatal if untreated. Major vessels affected by atherosclerosis include terminals of the coronary arteries, larger branches of the carotid arteries, cerebral arteries, large arteries of the lower extremities, renal arteries, and mesenteric arteries. Atherosclerosis of the cerebral arteries is the major cause of stroke (brain infarct).

Ischemic (**coronary**) **heart disease** is usually caused by **coronary atherosclerosis**, which results in decreased blood flow to the myocardium. It may result (depending on its severity) in angina pectoris, myocardial infarction, chronic ischemic cardiopathy, or sudden cardiac death. Angioplasty is the current mode of treatment for partially clogged arteries, and bypass surgery is necessary for severely clogged arteries. The most dangerous condition is when the **anterior interventricular artery** (also known as the **left anterior descending artery**) becomes blocked close to its origin from the left

(*continued*)

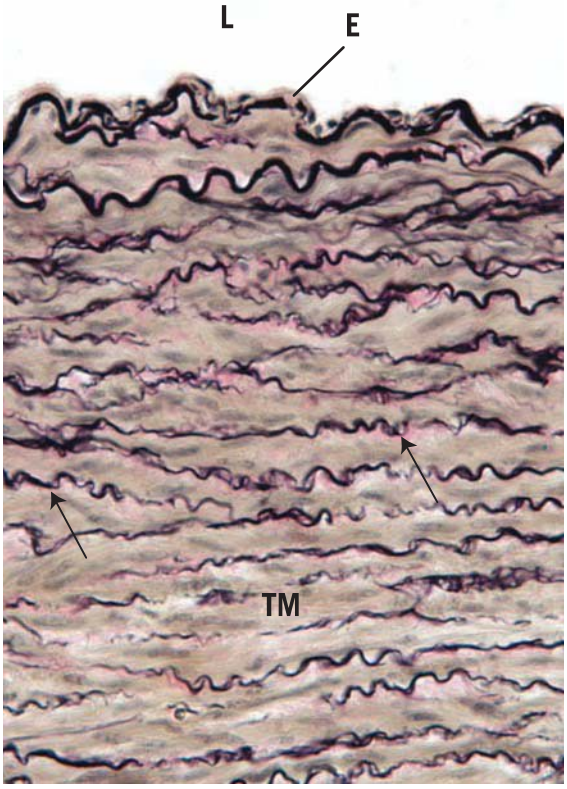


FIGURE 9.3. A light micrograph of the aorta (with elastic stain) at a higher magnification (×270). Observe the endothelial layer (E) adjacent to the lumen (L). Note that the tunica media (TM) contains an abundance of elastic fibers (*arrows*).

coronary artery because the anterior interventricular artery supplies the entire anterior wall of the heart. A complete blockage causes major damage to the myocardium with resultant death to the patient. Because of its frequently fatal complications, the anterior interventricular artery is also referred to as the "widow maker." Although blockage of this vessel occurs more frequently in males than in females, both genders are susceptible to blockage of the coronary arteries.

2. **Muscular arteries** (**distributing arteries**) distribute blood to various organs. These medium-sized arteries are smaller than elastic arteries but larger than arterioles and include most of the **named** arteries of the human body. They have a thick tunica media composed of layers of smooth muscle cells. Larger muscular arteries possess an **external elastic lamina** separating their boundary with the tunica adventitia (Fig. 9.4), which houses the vasa vasorum. The tunica intima is characterized by its endothelium and a prominent subendothelial **internal elastic lamina**.
3. **Arterioles** regulate blood pressure and are the terminal arterial vessels. They are the **smallest** arteries, with diameters less than 0.1 mm and a narrow lumen; their luminal diameter usually equals the wall thickness. The tunica adventitia of arterioles is scant, whereas the tunica media consists of up to two layers of smooth muscle. Their tunica intima consists of an endothelium, basal lamina, and scant amounts of connective tissue.

CLINICAL CONSIDERATIONS

Vasoconstriction primarily involves **arterioles** and reduces blood flow to a local region. Vasoconstriction is stimulated by **sympathetic nerve fibers** via vasomotor nerves. These nerves do not synapse on the muscle cells of the tunica media; rather they discharge the neurotransmitter norepinephrine that diffuses throughout the muscle layer and induces contraction of cells via gap junctions that reduce luminal diameter. It is at the level of arterioles that blood pressure can be controlled very rapidly.

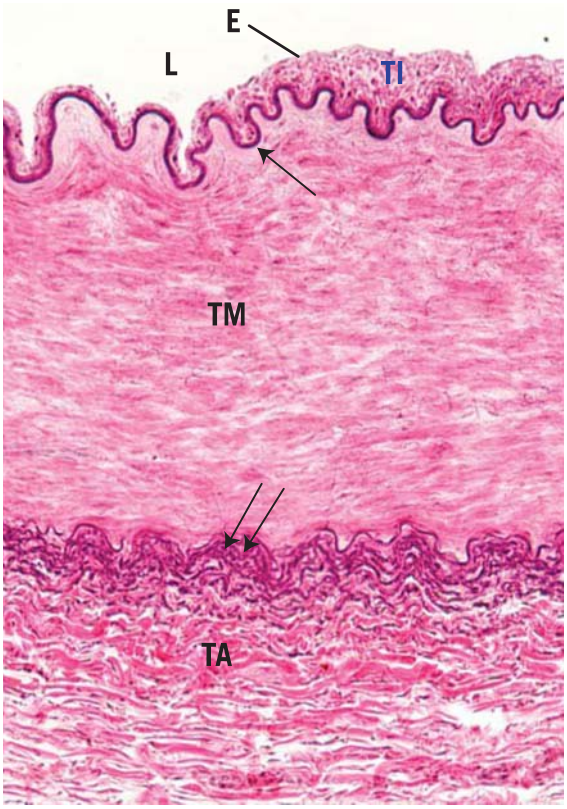


FIGURE 9.4. Light micrograph of an artery (×132). Observe the lumen (L), endothelial layer (E), internal elastic lamina (*single arrow*), tunica intima (TI), tunica media (TM), external elastic lamina (*double arrows*), and tunica adventitia (TA).

Vasodilation is accomplished by **parasympathetic nerve fibers** as follows: Acetylcholine released from these nerve terminals stimulates the endothelium to release **nitric oxide** (previously known as endothelial-derived relaxing factor [EDRF]). **Nitric oxide** diffuses to smooth muscle cells in the vessel wall and activates their cyclic guanosine monophosphate (cGMP) system, resulting in relaxation, which dilates the lumen.

4. **Metarterioles** (~8 μm in diameter) are narrow vessels arising from arterioles that give rise to capillaries. They are surrounded by incomplete rings of smooth muscle cells and possess individual smooth muscle cells (**precapillary sphincters**) that surround capillaries at their origin. Constriction of precapillary sphincters prevents blood from entering the capillary bed.

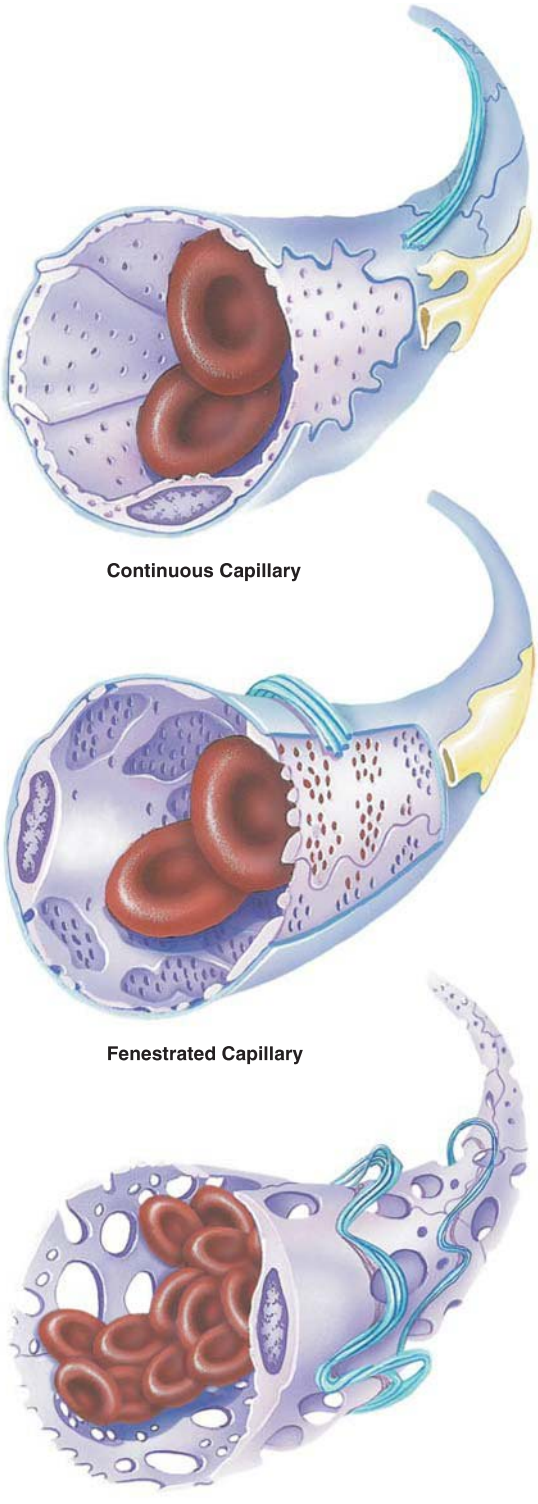
CLINICAL CONSIDERATIONS

Aneurysm is a **ballooning out of a blood vessel** that occurs because of a weakness in the arterial or venous wall, which may result in rupture. Arterial aneurysms may result from age-related displacement of elastic fibers by collagen. Aneurysms may be associated with **atherosclerosis** and **syphilis**. Atherosclerosis, especially of the abdominal aorta, may be due to genetic connective tissue disorders such as Marfan syndrome or Ehlers–Danlos syndrome.

Dissecting aneurysms are most often located in the ascending aorta and are represented by a longitudinal tear in the wall characterized by tearing of the elastic and muscular tissues, resulting in rupture into the pericardial sac. These conditions can be life-threatening because a weakness in an arterial wall may cause the artery to burst.

C. **Capillaries are small vessels (about 8–10 μm in diameter and usually less than 1 mm long).** Capillaries exhibit **selective permeability**, permitting the exchange of oxygen, carbon dioxide, metabolites, nutrients, metabolic wastes, signaling molecules, hormones, and other substances between the blood and tissues. They form **capillary beds** interposed between arterioles and venules.

1. **Capillary endothelial cells** form a single layer of cells arranged as a continuum in the shape of a cylinder, whose luminal diameter sometimes accommodates only one red blood cell at a time. Endothelial cells are surrounded by a basal lamina and occasional **pericytes**. Endothelial cells are nucleated, polygonal cells with an attenuated cytoplasm; they possess a Golgi complex, ribosomes, mitochondria, and some rough endoplasmic reticulum (RER); they contain pinocytotic vesicles. These cells possess intermediate filaments **desmin** or **vimentin** or both in the perinuclear zone, which provide a supportive function. Generally, endothelial cells are joined to each other by **fasciae occludentes** (tight junctions) along with some desmosomes and gap junctions.
2. The **three types of capillaries** are categorized depending on the structure of their endothelial cells and the continuity of the basal lamina (Fig. 9.5).
   a. **Continuous** (**somatic**) **capillaries** lack fenestrae and have a **continuous** basal lamina; they contain numerous **pinocytotic vesicles** except in the central nervous system (CNS), where they contain only a limited number of pinocytotic vesicles. They are located in nervous tissue, muscle, connective tissue, exocrine glands, and the lungs.
   b. **Fenestrated** (**visceral**) **capillaries** are formed from endothelial cells that are perforated with **fenestrae**. These openings are 60 to 80 nm in diameter and are **bridged by a diaphragm** thinner than a cell membrane; in the renal glomerulus, the fenestrae are larger and lack a diaphragm. They have a **continuous** basal lamina and few pinocytotic vesicles and are located in endocrine glands, the intestine, the pancreas, and the glomeruli of kidneys.
   c. **Sinusoidal capillaries** have a large lumen (30–40 μm in diameter), possess many large **fenestrae that lack diaphragms**, have a **discontinuous** basal lamina, and lack pinocytotic vesicles; gaps may be present at the cell junctions, permitting leakage between endothelial cells. They are located in the liver, spleen, bone marrow, lymph nodes, and adrenal cortex.
3. **Permeability of capillaries** is dependent on the morphology of their endothelial cells and on the size, charge, and shape of the traversing molecules. Permeability is altered during the inflammatory response by pharmacologically active substances, such as **histamine** and **bradykinin**.
   a. Certain substances **diffuse**, whereas others are **actively transported** across the plasma membrane of capillary endothelial cells.
   b. Other substances move across capillary walls via **small pores** (intercellular junctions) or **large pores** (fenestrae and pinocytotic vesicles).
   c. **Leukocytes** leave the bloodstream to enter the tissue spaces by penetrating intercellular junctions. This process is called **diapedesis**.
4. **Metabolic functions of capillaries** are carried out by the **endothelial cells** (Table 9.2):
   a. They **convert** inactive angiotensin I to active angiotensin II (especially in the lung). This powerful vasoconstrictor also stimulates secretion of the hormone aldosterone from the suprarenal gland, which promotes water retention.
   b. They **deactivate** various pharmacologically active substances (e.g., bradykinin, serotonin, thrombin, norepinephrine, prostaglandins).
   c. They **break down lipoproteins** to yield triglycerides and cholesterol.
   d. They **release prostacyclin**, a potent vasodilator and inhibitor of intravascular platelet aggregation.
   e. They **release** relaxing factor (**nitrous oxide**) and contraction factor (**endothelin 1**).
   f. They **regulate** transendothelial migration of inflammatory cells (**neutrophils**).
   g. They **release** tissue factors, facilitating blood coagulation.
5. **Blood flow to capillary beds** occurs either from **metarterioles** (with precapillary sphincters) or from **terminal arterioles** (Fig. 9.6).
   a. **Central channels** are vessels that traverse a capillary bed and connect arterioles to small venules. Their proximal portion is the **metarteriole**, possessing precapillary sphincters, and their distal portion is the **thoroughfare channel**, with no precapillary sphincter (Fig. 9.6).
   b. Metarterioles supply blood to the capillary bed, whereas thoroughfare channels receive blood from capillary beds.
   c. Contraction of precapillary sphincters forces the blood to flow from the **metarteriole** directly into the **thoroughfare channel**, thus bypassing the capillary bed and draining into a postcapillary venule.



Capillaries consist of a simple squamous epithelium rolled into a narrow cylinder 8–10 μm in diameter**. Continuous (somatic) capillaries** have no fenestrae; material traverses the endothelial cell in either direction via **pinocytotic vesicles. Fenestrated (visceral) capillaries** are characterized by the presence of perforations, **fenestrae**, 60–80 μm in diameter, which may or may not be bridged by a diaphragm**. Sinusoidal capillaries** have a large lumen (30–40 μm in diameter), possess numerous fenestrae, have discontinuous basal lamina, and lack pinocytotic vesicles. Frequently, adjacent endothelial cells of sinusoidal capillaries overlap one another in an incomplete fashion**.**

FIGURE 9.5. The three types of capillaries. (Reprinted with permission from Gartner LP. *Color Atlas of Histology.* 7th ed. Baltimore, MD: Wolters Kluwer; 2018:213.)

table 9.2 Endothelial Cell Functions

Function	Principal Locations	Mode of Action	Notations
Permeability	Capillaries and postcapillary venules	Paracellular, transcellular	Between cells; caveolae, VVO,* diapedesis
Hemostasis promotion	Throughout the vascular system	Release of tissue factor, vWF, plasminogen activator inhibitor, and protease-activated receptors	Weibel–Palade bodies house both vWF and tissue factor. If the integrity of the vascular endothelium is compromised those factors are released in order to form a blood clot and stop the escape of blood from the vessel
Hemostasis inhibition	Throughout the vascular system	Endothelial cells secrete and/or express tissue pathway factor inhibitor, thrombomodulin, heparin, plasminogen activator, prostacyclin, nitric oxide, and endothelial protein C receptor	These anticoagulants are always present in the normal, intact endothelium and prevent coagulation to ensure that blood remains in a fluid state
Vasomotor	Arterioles	*Vasodilation:* NO,† prostacyclin *Vasoconstriction:* endothelins 1, 2, and 3; prostaglandins; thromboxane A_2; and angiotensin II	Vasodilator and vasoconstrictor molecules are released in response to local or systemic factors; angiotensin II is produced by the conversion of angiotensin I by the endothelial cell membrane-bound ACE
Thermoregulation	Microcirculation in the dermis and bronchial tree	The close proximity of capillary beds to the surface of the skin and the luminal bronchial surface permits heat exchange with the external environment	Vasoconstriction reduces blood flow into the capillary beds, thus conserving body heat. Vasodilation increases blood flow into capillary beds, thus releasing body heat
Leukocyte trafficking	Postcapillary (HEVs)	L-selectins, chemokine receptor 7, and lymphocyte-associated antigens of lymphocytes interact with peripheral node addressin, chemokine ligand 21, and intercellular adhesion molecules of endothelial cells of HEVs which facilitate the migration of lymphocytes into the stroma of secondary lymphoid organs	Similar method permits the migration of other leukocytes out of postcapillary venules (non-HEVs) during the inflammatory process
Angiogenesis	Throughout the vascular system	Vascular endothelial growth factors released by endothelial cells and angiogenic factors released by tumor cells prompt other endothelial cells as well as pericytes to proliferate and form endothelial tubes that will eventually develop their own tunica media and tunica adventitia	Repairs vascular damage during wound healing as well as providing tor vascularization of growing tumors
Angiotensin II formation	Mostly in lung capillary beds	ACE converts angiotensin I to the potent vascular smooth muscle contractant angiotensin II	Angiotensin II elevates blood pressure, thereby increasing glomerular filtration rate and facilitates additional resorption of sodium from the ultrafiltrate

ACE, angiotensin-converting enzyme; HEV, high endothelial venules; NO, nitric oxide; vWF, von Willebrand factor.
*VVO—vesicular–vacuolar organelles are believed to be aggregates of fused caveoli.
†NO was known as endothelial-derived relaxing factor (EDRF); according to some authors, prostacyclin is also considered to be EDRF.

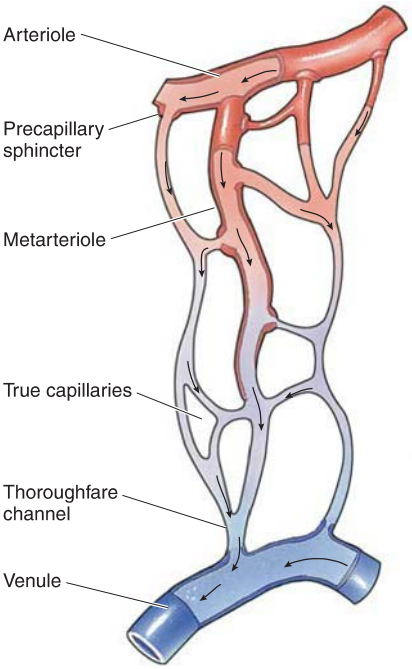


FIGURE 9.6. Blood flow to capillary beds. Some capillary beds, such as those of the skin, can be bypassed under certain circumstances. One method of controlling blood flow is the use of **central channels** that convey blood from an arteriole to a venule. The proximal half of the central channel is a **metarteriole**, a vessel with an incomplete smooth muscle coat. Flow of blood into each capillary that arises from the metarteriole is controlled by a smooth muscle cell, the **precapillary sphincter**. The distal half of the central channel is the **thoroughfare channel**, which has no smooth muscle cells and which accepts blood from the capillary bed. If the capillary bed is to be bypassed, the precapillary sphincters contract, preventing blood flow into the capillary bed, and the blood goes directly into the venule. (Reprinted with permission from Gartner LP. *Color Atlas of Histology*. 7th ed. Baltimore, MD: Wolters Kluwer; 2018:213.)

6. **Arteriovenous shunts** (**AV anastomoses**) are small vessels that connect arterioles directly to venules, bypassing the capillary bed. They function in **thermoregulation**, especially in the skin where they are abundant. These anastomoses also control blood pressure and blood flow.

D. Veins conduct blood away from the organs and tissues and return it *to the heart*. Veins contain about 70% of the body's total blood volume at any given time. Their walls are composed of three layers: the **tunica intima** (inner), **tunica media** (middle), and **tunica adventitia** (outer), the thickest and most prominent. Vasa vasorum are more numerous in veins than in arteries. A distinct internal elastic lamina is also absent in veins. The components of these layers and the variations among different types of veins are summarized in Table 9.3.

1. **Comparison with arteries.** Veins have thinner walls and larger, more irregular lumina than the companion arteries. They may have valves in their lumina that prevent retrograde flow of the blood (Fig. 9.7).

table 9.3 Comparison of Tunicae in Different Types of Veins

Tunica Components	Large Veins	Medium and Small Veins	Venules
Intima			
Endothelium	+	+	+
Basal lamina	+	+	+
Valves	In some	In some	–
Subendothelial layer	+	+	–
Media			
Connective tissue	+	Reticular, elastic fibers	±
Smooth muscle cells	+	+	±
Adventitia			
Smooth muscle cells	Longitudinal bundles	–	–
Collagen layers with fibroblasts	+	+	+

+, present and prominent; ±, present but not prominent; –, absent.

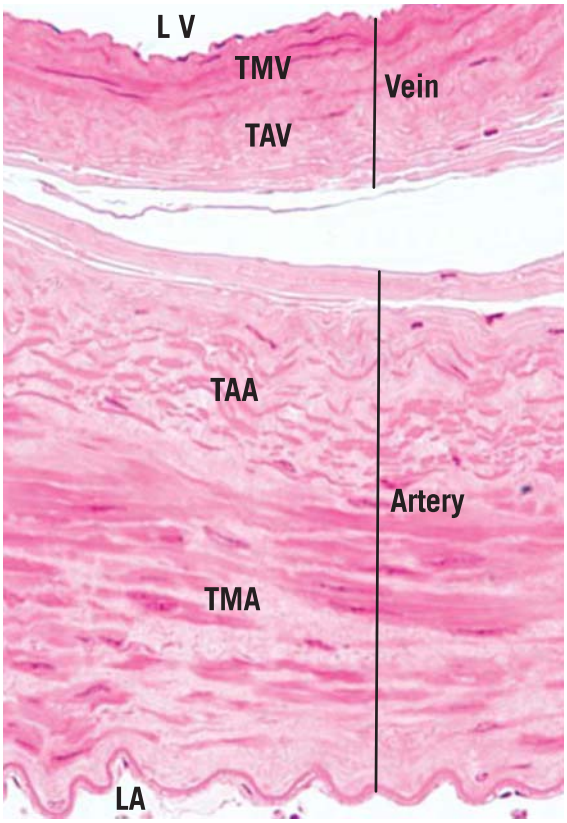


FIGURE 9.7. Light micrograph of an artery and vein (×270). LA, lumen of artery; LV, lumen of vein; TAA, tunica adventitia of the artery; TAV, tunica adventitia of the vein; TMA, tunica media of the artery; TMV, tunica media of the vein.

2. **Types of veins**
   a. **Large veins** include the vena cava and pulmonary veins. These veins possess **cardiac muscle** in the tunica adventitia for a short distance as they enter the heart. This layer also contains vasa vasorum and nerves.
   b. **Small and medium-sized veins** include the external jugular vein. These veins have a diameter of 1 to 9 mm.
   c. **Venules** have a diameter of 0.2 to 1 mm and are involved in **exchange of metabolites** with tissues and in **diapedesis** (the exiting of blood cells through the vessel wall).

CLINICAL CONSIDERATIONS

Varicose veins are abnormally tortuous **dilated veins**, present usually in the **leg**. They are caused by a decline in muscle tone, degenerative alteration of the vessel wall, and valvular incompetence. They generally occur in older people, being most prevalent in women, especially during pregnancy. Varicose veins of the anorectal junction are known as **hemorrhoids**.

E. **Specialized sensory mechanisms within arteries include three types of sensors: the *carotid sinus*, *carotid body*, and the aortic bodies (Table 9.4).**
   1. The **carotid sinus** is a **baroreceptor** located in the wall of the internal carotid artery just as it begins at the common carotid artery. Sensory endings of the glossopharyngeal nerve embedded within the wall of the artery are sensitive to changes in pressure that distend the vessel, thus initiating a signal to the vasomotor center of the brain. The resultant response triggers adjustments to the tension on the arterial wall via the smooth muscles of the tunica media, effecting changes in blood pressure.
   2. The **carotid body** is a **chemoreceptor** at the bifurcation of the common carotid artery. Specialized nerve endings of the vagus and glossopharyngeal cranial nerves are sensitive to oxygen and carbon dioxide levels as well as H^+ concentration. Glomus (type I) cells and sheath (type II) cells, which envelop the glomus cells, constitute the parenchyma. Nerve endings lose their Schwann cells upon entering the parenchyma, becoming covered instead by sheath cells. Impulses are shuttled to the brain by these two cranial nerves for processing.

table 9.4 Arterial System Sensory Structures

Sensory Structure	Location	Function
Carotid sinus	Wall of proximal portion of the ICA	Baroreceptor; sensitive to changes in pressure that tends to distend the vessel
Carotid body	Vessel wall at the bifurcation of the CCA	Chemoreceptor; sensitive to levels of CO_2, O_2, and H^+
Aortic bodies	Wall of the arch of the aorta and the junction of the CCA and subclavian arteries	Chemoreceptor; sensitive to levels of CO_2, O_2, and H^+

CCA, common carotid artery; ICA, internal carotid artery.

3. **Aortic bodies** are located in the wall of the arch of the aorta at the junction of the common carotid and subclavian arteries. Their structure and function are similar to those of the carotid body.
4. **Hormonal response to low blood pressure or volume starts with the kidney.**
   a. **Kidneys produce renin**.
   b. Renin cleaves the protein **angiotensinogen** circulating in the blood, forming angiotensin I, a mild vasoconstrictor.
   c. **Angiotensin I** is converted into **angiotensin II** by **angiotensin-converting enzyme** (**ACE**), located on the luminal plasmalemma of capillary endothelia (especially capillaries of the lungs).
   d. Angiotensin II, a potent vasoconstrictor, causes the walls of arterioles to contract, which raises blood pressure.
   e. Antidiuretic hormone (ADH), or vasopressin, secreted by the pituitary gland, is another potent vasoconstrictor released by the pituitary gland after severe hemorrhage.

II. OVERVIEW—LYMPHATIC VASCULAR SYSTEM

This system consists of peripheral lymphatic capillaries, lymphatic vessels of gradually increasing size, and lymphatic ducts. The lymphatic vascular system **collects excess extracellular fluid (lymph) and returns it to the venous portion of the cardiovascular system**. It drains most tissues with the exception of the nervous system and bone marrow.

A. **Lymphatic capillaries are thin-walled vessels that begin as *blind-ended channels* (e.g., *lacteals*) adjacent to capillary beds where they collect extracellular fluid.**
   1. They are composed of a single layer of **attenuated endothelial cells** that lack fenestrae and fasciae occludentes. They possess a sparse basal lamina.
   2. Extracellular fluid enters these low-pressure leaky capillaries via spaces between overlapping endothelial cells; once in the lumina of these vessels the fluid is known as lymph.
   3. Small lymphatic anchoring filaments between the surrounding connective tissue and the abluminal plasma membrane assist in maintaining luminal patency of these delicate vessels.

B. **Large lymphatic vessels possess valves and are similar in structure to small veins, except that they have larger lumina and thinner walls.**
   1. Lymph nodes that filter the lymph are interposed along their routes.
   2. These vessels converge to form the **thoracic duct** and **right lymphatic duct**. The thoracic duct empties into the venous system at the junction of the left internal jugular vein with the subclavian vein, whereas the right lymphatic duct empties into the venous system at a similar location on the right side of the neck.

CLINICAL CONSIDERATIONS

Edema, a pathologic process resulting in an **increased volume of extracellular fluid**, may be caused by venous obstruction or decreased venous blood flow (as in congestive heart failure), increased capillary permeability (because of injury), starvation, excessive release of histamine, and obstruction of lymphatic vessels. It is common during pregnancy and in older individuals. Edema that is responsive to localized pressure (i.e., depressions persist after release of pressure) is called **pitting edema**. Edema can be a symptom of a serious underlying disorder including heart disease; liver disease; or diseases of the thyroid, lymphoid system, or the kidneys, with debilitating consequences.

Review Test

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or completions of the statement. Select the ONE lettered answer that is BEST in each case.

1. A patient complains of shortness of breath even after only mild exercise. She states that she has had this condition for 2 years but recently has noticed that it has become more pronounced. Her medical history indicates that she had rheumatic fever when she was a child. Auscultation indicates an enlarged heart. What may the physician expect to find with other diagnostic tests?

(A) Mitral valve stenosis
(B) Tetralogy of Fallot
(C) Pulmonary artery aneurysm
(D) Coronary heart disease
(E) Ischemic heart disease

2. A cardiologist suspects that her patient has ischemic heart disease; therefore, she requests that the laboratory perform the proper diagnostic tests. What results does the internist expect to see?

(A) Malformed semilunar valve
(B) Atherosclerosis of coronary arteries
(C) Irregular heartbeat
(D) Faulty tricuspid valve
(E) Faulty bicuspid valve

3. Ischemic heart disease is the usual sequela to which condition?

(A) Bicuspid valve malfunction
(B) Abdominal aortic aneurysm
(C) Rheumatic fever
(D) Varicose veins
(E) Atherosclerosis

4. A cardiologist places a stent in a vessel commonly known as "the widow maker." What region of the heart is perfused by the branches of this vessel?

(A) Anterior wall of the heart
(B) Posterior wall of the heart
(C) Right side of the heart
(D) Left side of the heart
(E) Apex of the heart

5. A particular medication prescribed to a patient cannot cross the blood–brain barrier because capillaries in the CNS have which of the following characteristics?

(A) Discontinuous basal lamina
(B) Fenestrae with diaphragms
(C) Fenestrae without diaphragms
(D) Fasciae occludentes
(E) No basement membrane

6. A pregnant patient complains to her gynecologist about her hemorrhoids and asks what they are. The gynecologist explains that hemorrhoids occur frequently in women who are pregnant and they are merely:

(A) deformed arteries.
(B) arteriovenous shunts.
(C) thoroughfare channels.
(D) varicose veins.
(E) dilated arterioles.

7. A patient with hypertension and diabetes had a magnetic resonance imaging (MRI) of his kidneys, which showed signs of calcifications in the tunica media of the smaller arteries and arterioles of his kidney. What is the probable diagnosis?

(A) Arteriosclerosis
(B) Abdominal aortic aneurysm
(C) Rheumatic fever
(D) Varicose veins
(E) End-stage renal disease

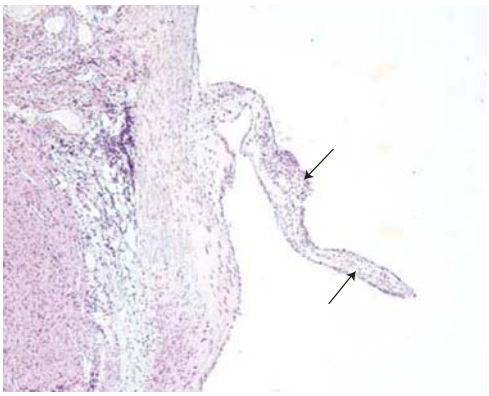
8. Which of the following vessels is most responsible for maintaining blood pressure?

(A) Aorta
(B) Muscular arteries
(C) Arterioles
(D) Metarterioles
(E) Large veins

9. Vasa vasorum function in a way that is similar to

(A) AV valves.
(B) semilunar valves.
(C) coronary arteries.
(D) elastic arteries.
(E) metarterioles.

Question 10 is based on the photomicrograph below:



10. Histopathology revealed that the deceased individual had scarring of the structure indicated by the arrows caused by a childhood disease. What was the probable cause of death of this individual?

(A) Mitral valve stenosis
(B) Tetralogy of Fallot
(C) Pulmonary artery aneurysm
(D) Coronary heart disease
(E) Ischemic heart disease

Answers and Explanations

1. **A.** A person who has had rheumatic fever as a child may develop heart valve disease later in life. Although the mitral valve is the one most commonly affected, the other valves may also be involved. The mitral valve becomes inflamed, fibrotic, and eventually incompetent or stenotic. This condition leads to respiratory hypertension and edema, which restricts respiratory function. The key is a history of rheumatic fever, because those individuals are predisposed to developing heart valve diseases.
2. **B.** Diagnostic tests for ischemic heart disease should reveal atherosclerosis of the coronary vessels. The internist tells her patient that if corrective measures are not employed, over time, excessive plaque composed of cholesterol and fats would be layered beneath the intima of these vessels, thus restricting blood flow to the myocardium of the heart, leading to angina pectoris, an infarction, or perhaps sudden death.
3. **E.** Ischemic heart disease is usually caused by coronary atherosclerosis, resulting in decreased blood flow to the myocardium. It may develop into angina pectoris, myocardial infarction, chronic ischemic cardiopathy, or sudden cardiac death.
4. **A.** The vessel of the heart commonly known as the "widow maker" is the anterior descending branch of the left coronary artery and it supplies the entire anterior wall of the heart.
5. **D.** Capillaries in the CNS are of the continuous type and thus lack fenestrae but have a continuous basal lamina and very tight fasciae occludentes. This characteristic is mostly responsible for the blood–brain barrier.
6. **D.** Hemorrhoids are varicose veins that are located at the anorectal junction. They are prevalent in pregnant women as well as in older adults.
7. **A.** Arteriosclerosis is characterized by rigidity and hyaline thickening of the blood vessel walls. It may involve the media of medium-sized arteries and eventual calcification in the media. Hyaline thickening usually attacks small arteries and arterioles in the kidneys and is usually associated with hypertension and diabetes mellitus.
8. **C.** Because arterioles as a whole have the largest volume in the arterial aspect of the vascular system and because they are very muscular, they have the ability to control blood pressure more than any other category of blood vessel.
9. **C.** Vasa vasorum are small blood vessels that supply the walls of elastic and muscular arteries with oxygen and nutrients just as the coronary arteries provide for the walls of the heart.
10. **A.** The childhood disease was group A β-hemolytic streptococcal infection that caused scarring of the mitral valve, resulting in stenosis of the mitral valve and eventual death of the patient.

chapter 10

Lymphoid System

I. OVERVIEW—LYMPHOID (IMMUNE) SYSTEM

A. The lymphoid system consists of *capsulated lymphoid organs* (thymus, spleen, tonsils, and lymph nodes), *diffuse lymphoid tissue*, and *lymphoid cells* (composed primarily of T lymphocytes, B lymphocytes, and macrophages). Capsulated lymphoid organs are of two types: primary lymphoid organs and secondary lymphoid organs. **Primary lymphoid organs** (bone marrow and thymus) "educate" lymphocytes so that they become immunocompetent cells. **Secondary lymphoid organs** (diffuse lymphoid tissue, lymph nodes, spleen, and tonsils) sequester immunogens and allow immunocompetent cells and antigen-presenting cells (APCs) to interact with the immunogens and with each other to initiate an immune reaction and eliminate the antigenic attack.

B. The immune system has two components, the innate immune system (nonspecific) and the adaptive immune system (specific).

1. The **innate immune system** has no immunologic memory; it acts rapidly, but in a nonspecific manner. Its chief constituents are complement proteins, toll-like receptors (TLRs), and natural (polyreactive) antibodies, which are discussed here, whereas the other components, mast cells, eosinophils, neutrophils, macrophages, and natural killer cells (NK cells), are discussed later in this chapter.
   a. **Complement proteins** are blood-borne proteins (C1–C9) that function in nonspecific host defense and initiate the inflammatory process.
   b. **TLRs** in humans are a family of at least 11 receptors that are integral proteins located either in the cell membranes or in the membranes of endosomes, of specific cells of the innate immune system (Table 10.1). TLRs have key functions in the recognition of repeating molecular patterns that exist in pathogens, known as **pathogen-associated molecular patterns** (**PAMPs**), and each TLR pair recognizes PAMPs that are specific to them. Most TLR pairs are **homodimers** (e.g., composed of identical TLRs), but some are **heterodimers** (composed of different TLRs).
      (1) TLRs 1, 2, 4, 5, 6, 10, and 11 are integral proteins of the cell membrane and recognize molecular patterns belonging to bacteria, protozoa, and fungi, whereas TLRs 3, 7, 8, and 9 are integral proteins of endosomal membranes and recognize molecular patterns belonging to nucleic acids of viruses (and some other microorganisms). For instance, TLR4 recognizes lipopolysaccharides of gram-negative bacteria, and TLR2 recognizes peptidoglycan of gram-positive bacteria. Once these receptors bind to their ligand, they cause the release of **tumor necrosis factor-α** (**TNF-α**); **interleukins 1 and 12** (**IL-1 and IL-12**); and other systemic inflammation-inducing **cytokines**, which can initiate an ***adaptive*** immune response.
      (2) Most TLRs, including TLR4 and TLR2 as well as TNF-α and IL-1, activate the **NF-κB pathway** (**nuclear factor kappa-light chain enhancer of activated B cells**).
         (a) **NF-κB** is a family of five proteins that form dimers with each other (homodimers or heterodimers) that are closely bound by inhibitory proteins, known as **IκB**, which keep NF-κB in the inactive state.

table 10.1 TLRs, Their Location, and Function

Receptor	Location	Function
TLR1	*Cell membrane* of macrophages, neutrophils, B lymphocytes, and dendritic cells	In conjunction with TLR2, it binds to triacylated lipopeptides as well as to peptidoglycans of gram-positive bacteria Peptidoglycan coats of gram-negative bacteria are much thinner; therefore, the reactivity is much less pronounced
TLR2	*Cell membranes* of T reg cells, B lymphocytes, dendritic cells, and macrophages	Binds to lipoteichoic acid of gram-positive bacteria as well as to various lipopeptides and lipoproteins of various bacteria, and to zymosan of fungi. In conjunction with TLR6 it binds to diacylated lipopeptides. See its binding abilities in conjunction with TLR1 in the row above
TLR3	*Endosomes* of macrophages and dendritic cells	Binds to double-stranded viral RNA
TLR4	*Cell membranes* of macrophages, dendritic cells, neutrophils, and endothelial cells	Binds to the endotoxin LPS of gram-negative bacteria but requires the homodimers state along with the presence of MD2 in order to recognize LPS
TLR5	*Cell membranes* of macrophages, dendritic cells, and intestinal epithelial cells	Binds to the protein flagellin of bacterial flagella
TLR6	*Cell membranes* of macrophages, mast cells, and B lymphocytes	Binds to lipopeptides of the bacteria-like organism, *Mycoplasma*; in conjunction with TLR2, it binds to diacylated lipopeptides
TLR7	*Endosomes* of specialized dendritic cells* and B lymphocytes	Binds to single-stranded viral RNA
TLR8	*Endosomes* of macrophages, dendritic cells, type I pneumocytes, and mast cells	Binds to single-stranded viral RNA
TLR9	*Endosomes* of macrophages, specialized dendritic cells*	Binds to bacterial and viral DNA
TLR10	*Cell membranes* of macrophages and dendritic cells	Possibly binds to profilin-like proteins of the parasite *Toxoplasma gondii*
TLR11	*Cell membranes* of macrophages; kidney and urinary bladder epithelial cells	Recognition of *T. gondii*

DNA, deoxyribonucleic acid; LPS, lipopolysaccharide; MD, myeloid differentiation factor; RNA, ribonucleic acid; TLR, toll-like receptor.
*Specialized dendritic cells are plasmacytoid dendritic cells that constitute less than 1% of mononuclear cells of the peripheral circulation. When activated, they release the antiviral agents IFN-α and IFN-β, and type I interferons.

(b) When TLR2 or TLR4, TNF-α, or IL-1 bind their ligands, they **activate a kinase** that phosphorylates IκB and releases NF-κB. The phosphorylated IκB become ubiquinated and are sent to **proteasomes** for destruction. The released **NF-κB** is translocated into the **nucleus**, where, in conjunction with a coactivator protein, it finds its target gene and **initiates its transcription**. The protein products of these genes activate **innate immune responses** and **inflammatory responses**.

CLINICAL CONSIDERATIONS

A correlation has been demonstrated between hypertension and TLR activity, especially TLR3 in preeclampsia and TLR2 and TLR4 in angiotensin II–induced hypertension. Although the mechanism of TLR action is not understood, preganglionic neurons of the central nervous system (CNS) possibly activate a sympathetic response that accounts for the increased state of hypertension.

c. **Natural** (**polyreactive**) **antibodies** are synthesized by a group of B cells even prior to birth. These antibodies are produced without the individual's having to be exposed to antigens; in fact, in mice reared in a germ-free environment, these natural antibodies are always present. They are polyreactive; that is, they can recognize a number of antigens and react against them. Natural antibodies are able to distinguish widespread molecular signatures (especially oxidized lipids, glycolipids, and membrane lipids) present on microbes and apoptotic cells.

CLINICAL CONSIDERATIONS

The ABO blood groups are due to the presence of specific glycolipids decorating the surfaces of erythrocytes. Each individual has **natural antibodies** against red blood cells that possess glycolipids other than those of the self. If the individual receives the incorrect blood type during a blood transfusion, the natural antibodies react against the donated blood and death may ensue.

Over 2 billion cells are killed or undergo apoptosis every day in every person. These dead or dying cells display specific membrane molecules that are not present on the surfaces of healthy cells, and natural antibodies bind to these molecules. In this fashion, natural antibodies mark these dead or dying cells for elimination by macrophages or dendritic cells.

Additionally, although specific molecules called lectins preferentially bind to the surfaces of pathogenic invaders, they cannot damage the pathogens. However, natural antibodies attach to the lectins, and the **lectin–natural antibody complex** activates the immune system to destroy the pathogen.

2. The **adaptive immune system** is evolutionarily more recent than the innate immune system. It possesses four characteristics: (1) ability to distinguish self from nonself, (2) memory, (3) specificity, and (4) diversity. The cells of the adaptive immune system, namely, T lymphocytes, B lymphocytes, and APCs, communicate with one another by the use of signaling molecules (**cytokines**) and cell surface markers (e.g., cluster of differentiation proteins), thus relaying information to each other in response to antigenic invasion.

C. The immune system functions **primarily to defend the organism by mounting *humoral immune responses* against foreign substances (*antigens*) and *cell-mediated immune responses* against microorganisms, tumor and transplanted cells, and virus-infected cells.**

CLINICAL CONSIDERATIONS

Individuals may suffer from congenital immunodeficiency disorders, usually a recessive X-linked genetic defect that affects males to a much greater extent than females. The most common symptoms are recurrent respiratory infections that have a tendency to progress to pneumonia. Additional indicators are multiple skin and oral infections, such as yeast infections of the mouth (thrush) or of the vagina. In some cases, such as X-linked agammaglobulinemia, B lymphocytes do not develop, resulting in scarcity of plasma cells and consequently lack of immunoglobulin production.

II. IMMUNE SYSTEM CELLS

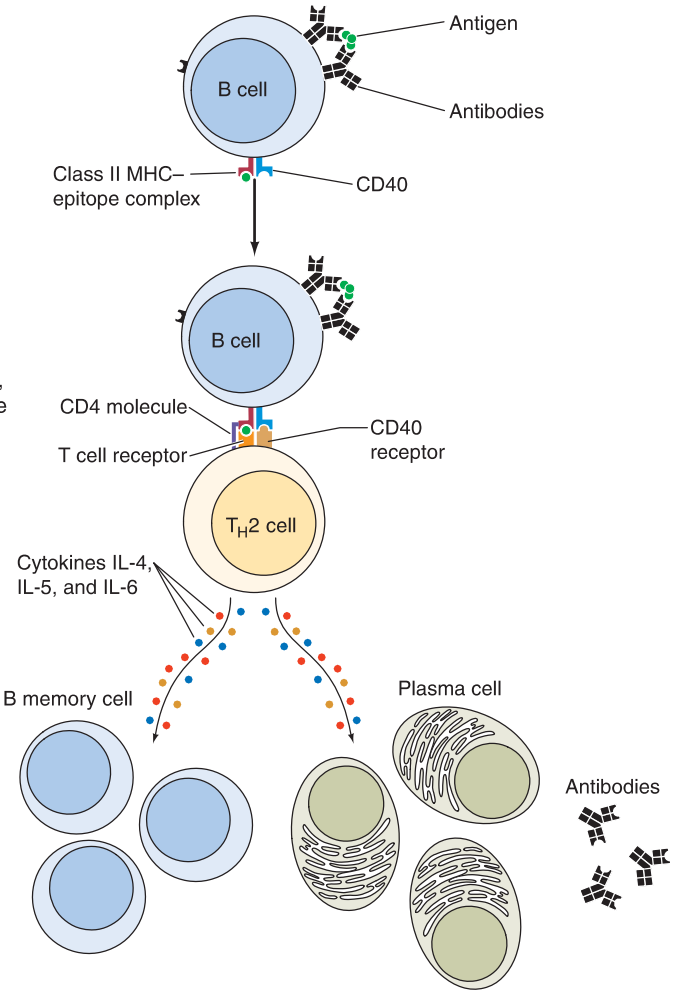
A. Overview—Cells of the immune system: T lymphocytes, B lymphocytes, and APCs

1. Cells of the immune system include clones of **T lymphocytes** (**T cells**) and **B lymphocytes** (**B cells**). A **clone** is composed of **identical** cells that can recognize and respond to a single or a small group of related antigenic determinants known as **epitopes** (that small portion of an antigen to which an **antibody** binds). A single antigen may have a number of epitopes, each different, recognized by different antibodies each of which is specific to each of those epitopes.
   - **a.** The region of the antibody that binds to an epitope is known as a **paratope**. Note that, instead of recognizing entire antigens, antibodies recognize only those portions of antigens that act as epitopes.
   - **b.** Exposure to antigen and one or more **cytokines** induces **activation** of **resting T cells** and **B cells**, leading to their proliferation and differentiation into **effector cells** (Fig. 10.1). Both B cells and T cells arise in the bone marrow; T cells leave the bone marrow to mature in the thymus, whereas B cells remain in and mature in the bone marrow.
2. **APCs** (e.g., macrophages, lymphoid dendritic cells, Langerhans cells, follicular dendritic cells, M cells, and B cells), **mast cells**, and **granulocytes** are also cells of the immune system. (Note that although B cells can present epitopes to T cells and are thus APCs, their role in this function is probably limited to the secondary [anamnestic] immune response rather than the primary immune response.)

Antigen-dependent cross-linking of the surface antibodies activates the B cell, which places the epitope–MHC II complex on the external aspect of its plasmalemma.

The TCR and CD4 molecules of the T_H2 cell recognize the B cell's MHC II–epitope complex. In addition, binding of the B cell's CD40 molecule to the T_H2 cell's CD40 receptor induces the B cell to proliferate and the T_H2 cell to release of IL-4, IL-5, and IL-6.

IL-4, IL-5, and IL-6 induce the activation of B cells and their differentiation into B memory and plasma cells.



A

FIGURE 10.1. Schematic overview of the interactions among the various cells of the immune system. **A.** Thymic-dependent antigen-induced B memory and plasma cell formation. **B.** Cytotoxic T lymphocyte activation and cell killing. **C.** Macrophage activation by T_H1 cells. APCs, antigen-presenting cells; CD, cluster of differentiation; CTL, cytotoxic T lymphocytes; IL, interleukin; IFN, interferon; MHC, major histocompatibility complex; TCR, T-cell receptors; T_H, T helper cells. (Adapted with permission from Gartner LP. *Textbook of Histology*. 4th ed. Philadelphia, PA: Elsevier; 2017:326, 328.)

B. T lymphocytes

1. Overview

a. T lymphocytes include several functionally distinct subtypes and are responsible for **cell-mediated immune responses**. Also, they assist B cells in developing humoral responses to **thymic-dependent antigens**. T cells have various surface markers, including **cluster of differentiation molecules** (**CD molecules**).

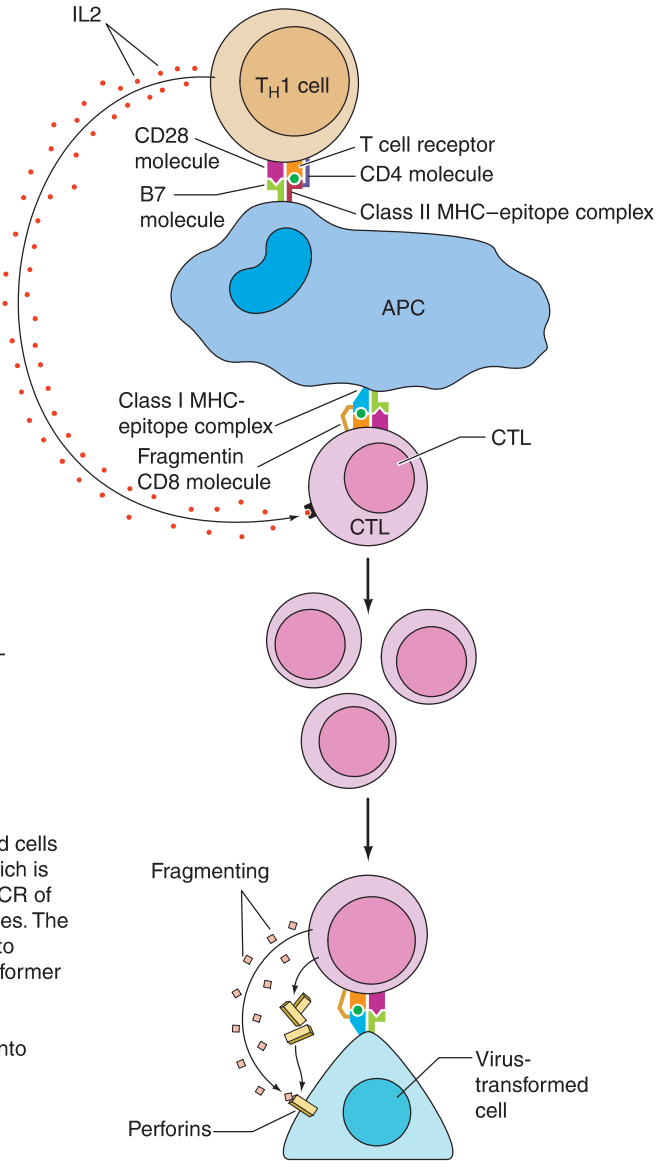
b. **T-cell receptors** (**TCRs**) are heterodimers, that is, they are composed of two dissimilar protein chains: **α and β** or **γ and δ**. TCRs are present only on the surfaces of T lymphocytes and are always associated with a CD3 molecule. Although they belong to the **Ig** (**immunoglobulin**) **superfamily**, unlike Igs, they are not secreted. TCRs can recognize only **protein** antigens, and only if APCs present the epitopes to them.

(1) **γ/δ T cells** are more uniform, are much fewer in number, do not form memory T cells, and are usually located in the intestinal mucosa; they react to antigens that are indicative of microbial assault.

The TCR and CD4 molecule of the T_H1 cell binds to the epitope and the MHC II of the APC, respectively. The binding induces the APC to express B7 molecules on its plasmalemma, which then binds to the CD28 molecule of the T_H1 cell, inducing that cell to release IL-2.

The same APC expresses the MHC I-epitope complex, which is recognized by the CD8 molecule and the TCR of the CTL. In addition, the CD28 molecule of the CTL binds with the B7 molecule on the APC plasmalemma. These interactions induce the expression of IL-2 receptors on the CTL plasma membrane. Binding of IL-2 (released by the T_H1 cell) to the IL-2 receptors of the CTL induces that cell to proliferate.

The plasmalemma of virally transformed cells expresses MHC I–epitope complex, which is recognized by the CD8 molecule and TCR of the newly formed cytotoxic T lymphocytes. The binding of the CTL induces these cells to secrete perforins and fragmentins. The former assemble to form pores in the plasma membrane of the transformed cell, and fragmentin drives the transformed cell into apoptosis.



B

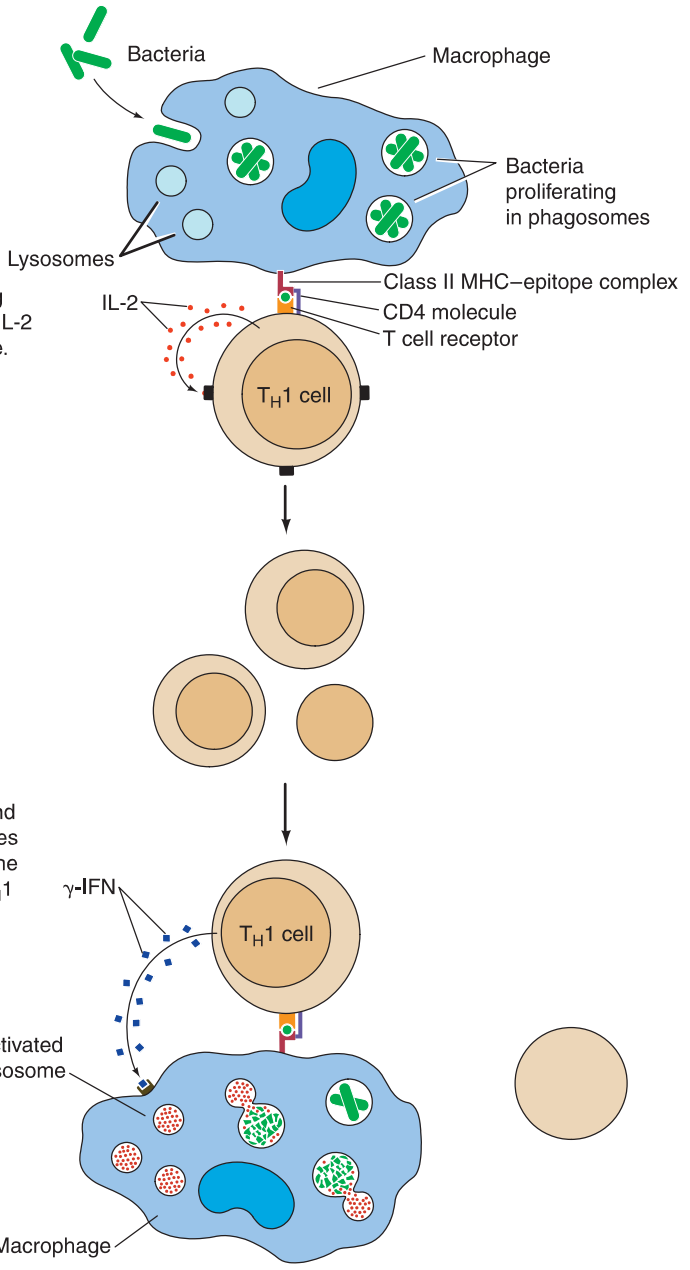
FIGURE 10.1. (*continued*)

(2) **α/β T cells** constitute the bulk of the T-cell population, form memory T cells, and, although they react slower than γ/δ T cells, they are responsible for most T-cell responses.

(3) The third group of T cells, known as **natural T killer cells** (**NKTs**), possess a limited number of **α/β TCRs**, and they recognize lipid antigens only.

c. Note that T cells do not recognize antigens; instead they recognize only **epitopes** that are bound to **major histocompatibility complex** (**MHC**) **molecules** on the surface of **APCs**. Because T cells require that the epitopes be presented in conjunction with MHC molecules, they are said to be **MHC restricted** (see Section III). The only exception to this rule is that NKT cells require the lipid antigen to be presented to them by **CD1 molecules**, rather than MHC molecules; thus, they are considered to be **CD1 restricted**.

2. Maturation of α/β T cells, γ/δ T cells, and NKT cells occurs in the thymus. Only **α/β T cells** spend a considerable time in the thymus and they go through a series of steps in their "education" to become immunocompetent cells. Although **γ/δ T cells** and **NKT cells** also spend some time in the thymus, their "education" to become immunocompetent cells is very sparse. This textbook



Bacteria-infected macrophages bear MHC II–epitope complexes on their plasmalemma that, if recognized by the CD4 molecule and TCR of T_H1 cells, activates these T cells, causing them to release IL-2 and to express IL-2 receptors on their plasma membrane. Binding of IL-2 to the IL-2 receptors induces proliferation of the T_H1 cells.

The TCR and CD4 molecules of the newly formed T_H1 cells recognize and bind to the MHC II–epitope complexes of bacteria-infected macrophages. The binding causes activation of these T_H1 cells so that they release γ-IFN, a cytokine that encourages the macrophages to destroy their endocytosed bacteria

C

FIGURE 10.1. (*continued*)

will describe the maturation only of α/β T cells, and they will be referred to simply as T cells (although NKT cells will also be discussed in a subsection below).

a. Immunoincompetent progenitor T lymphocytes migrate from the bone marrow to enter the thymus at the corticomedullary junction and migrate to the **outer region of the thymic cortex**. Once in the thymus, they are also referred to as **thymocytes**. These thymocytes have neither **CD4** nor **CD8** surface **markers** and, therefore, are known as **double negative T cells**. However, thymocyte plasmalemma possesses **Notch-1 receptors** that permit these thymocytes to respond to cytokines released by **thymic epithelial reticular cells** to become T cells.

b. Within the **outer thymic cortex**, thymocytes undergo **gene rearrangements** and begin to express integral membrane proteins: antigen-specific TCRs, CD4, and CD8 surface markers.

Because they express ***both*** CD4 and CD8 they are known as **double-positive T cells**. These cells are now **immunocompetent**.

c. Double-positive T cells that do not recognize **self-MHC–epitope complex molecules** offered to them by **epithelial reticular cells** of the thymic cortex are forced into apoptosis, because they failed to recognize the body's own MHC molecules and the body's own epitopes. Double-positive T cells that were able to recognize the self-MHC–epitope complex are permitted to enter the medulla of the thymus. Interestingly, 90% of the double-positive T cells die in the cortex.

d. Still in the **thymic cortex**:

(1) Those double-positive T cells that contact epithelial reticular cells that bear **MHC I–epitope complexes** stop expressing CD4 markers and become **single-positive T cells** that express only **CD8 markers**. In contrast, those double-positive T cells that contact epithelial reticular cells that bear **MHC II–epitope complexes** stop expressing CD8 markers and become **single-positive T cells** that express only **CD4 markers**.

(2) Those **single-positive T cells** that remain alive enter the **thymic medulla** as full-fledged immunocompetent, but **naïve**, **T cells**.

e. The final step in the maturation of T cells occurs in the **medulla of the thymus**, where there is another test: **Medullary epithelial reticular cells** present self-epitopes on MHC I and MHC II molecules to single-positive T cells. Those T cells whose TCRs bind to the MHC–epitope complex are forced into apoptosis to prevent a possible **autoimmune response**. The epithelial reticular cells also express the transcription factor **AIRE** (**a**uto**i**mmune **re**gulator), which assists in the recognition of certain tissue-specific antigens such as **insulin** and **filaggrin** (protein in the stratum corneum of skin), and force T cells, which would be triggered by these proteins to initiate an immune response, into apoptosis.

f. The T cells that survive this final test are permitted to leave the thymic medulla to be distributed by the circulatory system to various regions of the body. *The entire process of T-cell development and the eradication of such high percentage of T cells is to ensure that only the T cells that identify only non-self-epitopes presented by self-MHC molecules remain alive and are released into circulation.*

3. T lymphocyte subtypes. The three types of T cells are naïve, memory, and effector T cells. Some have a number of subtypes.

a. Naïve T cells are immunologically competent cells that have not as yet been activated (i.e., they have not come into contact with their designated antigen outside the thymic cortex), but possess CD45RA surface markers. Once activated, they undergo cell division and form both memory T cells and effector T cells.

b. Memory T cells, derived from naïve T cells, possess **CD45R0 surface molecules**. The two classes of these cells are central memory T cells (**TCMs**) ($CR7^+$) and effector memory T cells (**TEMs**) ($CR7^-$).

(1) TCMs express CR7 molecules on their surface. They reside in the paracortex of lymph nodes. If they interact with an epitope that they recognize when APCs present it to them, they cause the APC to release IL-12, which induces TCMs to undergo cell division, and the newly formed cells differentiate into effector T memory cells.

(2) TEMs do not express CR7 molecules on their surface. They migrate to inflammatory sites, where they undergo cell division and form **effector T cells**.

c. Effector T cells are derived from TEMs and are capable of initiating an immune response. The subtypes of effector T cells are T helper cells, cytotoxic T lymphocytes (CTLs, T killer cells), and regulatory T cells (T reg cells).

(1) T helper cells (T_H0, T_H1, T_H2, T17, and $T_H\alpha/\beta$) are **$CD4^+$** cells. After activation, these cells synthesize and release numerous growth factors known as **cytokines** (**lymphokines**). **T_H0 cells** differentiate into the other four types of T helper cells (Table 10.2).

(a) T_H1 cells regulate intracellular responses against viral or bacterial invasions and instruct macrophages in killing bacteria.

(b) T_H2 cells regulate humoral responses against parasites by stimulating B cells to produce IgE antibodies, and in the mucosa by stimulating B cells to produce IgA antibodies.

(c) T17 cells manufacture and release IL-17, which recruits neutrophils and enhances their bactericidal activities.

(d) $T_H\alpha/\beta$ cells release IL-10 as well as interferon α or β (IFN-α or β) to act against viruses.

table 10.2 Types of T Helper Cells and Their Function

T Helper Cell	Function
T_H0 cells	Differentiate into other T helper cells
T_H1 cells	Regulate intracellular responses against viral or bacterial invasions and instruct macrophages in killing bacteria
T_H2 cells	Regulate humoral responses against parasites by stimulating B cells to produce IgE antibodies, and, in the mucosa, by stimulating B cells to produce IgA antibodies
T17 cells	Release IL-17, which recruits neutrophils and enhances their bactericidal activities
$T_H\alpha/\beta$ cells	Release IL-10 as well as IFN-α or β to act against viruses

IFN, interferon; Ig, immunoglobulin; IL, interleukin.

(e) The cytokines **IL-4**, **IL-5**, and **IL-6** released by T_H2 cells induce B cells to proliferate and mature and thus respond to an antigenic stimulus, whereas **IL-10** activates NK cells and inhibits the formation of T_H1 cells, **IL-9** enhances the proliferation of T_H2 cells as well as mast cell responses, and **IL-13** retards T_H1 cell development and induces the development of B cells.

(f) Other cytokines produced by T_H1 cells, such as IL-2, interferon-γ (IFN γ), and others, **modulate the immune response** in diverse ways (Table 10.3). Macrophages synthesize and release IL-12, which restricts the development of T_H2 cells and encourages the formation of T_H1 cells.

table 10.3 Biologic Activities of Selected Cytokines in the Immune Response*

Cytokine	Secreted By	Target Cell	Action
IL-1α, IL-1β	Macrophages and epithelial cells	T cells, macrophages	Activates both T lymphocytes and macrophages
IL-2	T_H1 cells	Activated T cells, B cells	Induces mitosis of activated T and B cells
IL-4	T_H2 cells	B cells	Induces mitosis of B cells, their transformation into plasma cells, promotes isotype switching from IgM to IgG and IgE
IL-5	T_H2 cells	B cells	Induces mitosis, maturation of B cells; promotes isotype switching from IgM to IgE
IL-6	APCs and T_H2 cells	T cells, activated B cells	Activates T cells, induces maturation of B cells to IgG-forming plasma cells
IL-10	T_H2 cells	T_H1 cells	Inhibits formation T_H1 cells; retards their ability to manufacture cytokines
IL-12	B cells, macrophages	NK cells, T cells	Activates NK cells, facilitates formation of T_H1-like cells
IL-18	Macrophages	T_H1 cells and NK cells	Acts on T_H1 cells to produce IFN-γ and enhances NK cell activity
IL-23	Macrophages	$CD8^+$ T cells	Decreases the motility of $CD8^+$ T cells
TNF-α	Macrophages	Macrophages	Macrophages self-activate to manufacture, release IL-12
	T_H1 cells	Activated macrophages	Promotes production of oxygen radicals facilitating bacterial killing within endosomes of activated macrophages
IFN-α	Virally attacked cells	NK cells, macrophages	Activates macrophages, NK cells
IFN-β	Virally attacked cells	NK cells, macrophages	Activates macrophages, NK cells
IFN-γ	T_H1 cells	Macrophages, T cells	Activates cytotoxic T cells to kill altered and/or foreign cells; promotes phagocytosis by macrophages

APCs, antigen-presenting cells; CD, cluster of differentiation; Ig, immunoglobulin; IL, interleukin; IFN, interferon; NK, natural killer; T_H, T helper; TNF, tumor necrosis factor.
*See Chapter 5 for discussion of cytokines involved in hemopoiesis.

CLINICAL CONSIDERATIONS

Acquired immunodeficiency syndrome (**AIDS**) is caused by infection with **human immunodeficiency virus** (**HIV**), which preferentially invades T_H cells, causing a severe depression in their number and thus **suppressing both cell-mediated and humoral immune responses.**

AIDS is characterized by **secondary infections** by opportunistic microorganisms that cause pneumonia, toxoplasmosis, candidiasis, and other diseases. It is also characterized by the development of certain malignancies, such as **Kaposi sarcoma** and **non-Hodgkin lymphoma.**

(2) **T cytotoxic cells** are **$CD8^+$** cells. After priming by an antigenic stimulus via an APC, T cells are induced by **IL-2** to proliferate, forming new **CTLs,** which mediate (via **perforins** and **granzymes**) **apoptosis** of foreign cells as well as virally altered self-cells (Fig. 10.1).

CLINICAL CONSIDERATIONS

A relatively new method for treating advanced **acute lymphoblastic leukemia** (**ALL**), a disease in which lymphocytes (especially B cells) become malignant, involves what is known as **adoptive cell transfer** therapy, in which the patient's own T cells are removed and are genetically engineered to synthesize specific receptors that identify and bind to a particular cell surface antigen. These modified T cells, known as **chimeric antigen-receptor T cells** (**CAR T cells**) are instructed to proliferate in vitro and are then infused into the patient, where they continue to proliferate. In the case of ALL, the CAR T cells recognize and target CD19 molecules (and now also CD22 molecules) that are expressed on the surfaces of the malignant B cells, thereby killing those lymphocytes. Not only do these CAR T cells kill malignant B cells outside the CNS, but they are able to enter the CNS, where some of the malignant B cells "hide" to avoid chemotherapeutic drugs, and kill the cancer cells. Although still only in the clinical trial stage, adoptive cell transfer therapy has been shown to be exceptionally capable of eliminating cancer in some patients.

(3) **T reg cells** (previously called T suppressor cells) are **$CD4^+$** cells. T reg cells are of two types, natural and inducible.

(a) **Natural T reg cells** (**nT reg cells**) originate in the thymus, possess, in addition to the CD4 marker, **CD25** and **Foxp3** markers (**forkhead family transcription factor box p3**), and suppress the immune response in a non–antigen-specific manner. Naïve T cells are converted to natural T reg cells by dendritic cells of the thymus under the influence of the cytokine **thymic stromal lymphopoietin** (**TSLP**). Interestingly, among the richest sources of TSLP are the cells of **Hassall corpuscles** of the thymus, which has been implicated in inducing nT reg cell formation.

(b) **Inducible T reg cells** (also known as **T_H3 cells**) originate outside the thymus from naïve T cells. They inhibit the formation of T_H1 cells, thus suppressing the immune response.

CLINICAL CONSIDERATIONS

Individuals who have a genetic mutation that prevents their cells from performing **deoxyribonucleic acid** (**DNA**) **mismatch repair** (repairing errors that occur during DNA replication) have a greater incidence of certain cancers, particularly, cancers of the brain, pancreas, and large intestines. The malignant cells of these individuals place atypical proteins, **PD-L1** and **PD-L2** (**programmed death-ligand 1 and 2**) on their cell membranes, that are believed to suppress T cytotoxic cell (CTL) proliferation when they contact the PD-1 and PD-2 receptors of CTLs. Recent immune therapy clinical trials, using the antibody **pembrolizumab**, demonstrated that intravenous infusion of this antibody was able to block the **PD-1 receptors** (**programmed cell death protein 1 receptors**) of CTLs, allowing their proliferation and dissemination throughout the body to seek out and destroy the malignant cells. The tumors of most patients in the clinical trials who received pembrolizumab showed dramatic regression.

(4) **NKTs** are similar to NK cells except that they have to go to the thymus to become immunologically competent. They are unusual in that they recognize **lipid antigens** that are presented to them by APCs *in conjunction with a CD1 molecule*. NKTs manufacture and secrete IL-4, IL-10, and INF-γ, and sport a limited range of TCRs on their plasma membranes.

C. B lymphocytes

1. Overview

a. B lymphocytes originate and mature into **immunocompetent** cells within the bone marrow. They are responsible for the **humoral immune response**. These cells go through a series of developmental steps, from pre-B cells; through immature; and, finally, **transitional B cells** in which they express different light and heavy chains of immunoglobulins on their cell membranes. Transitional B cells travel to the spleen, where they either **die** or **undergo final maturation** and become mature B cells.

b. **Mature B cells** express immunoglobulins IgD and the monomeric form of IgM on the external aspect of their plasma membranes (known as **surface immunoglobulins** [**sIgs**]). In order to affix the sIgs in their cell membrane, they require the help of two pairs of proteins, known as **Igα** and **Igβ**; these proteins function not only in affixing the sIgs but also in transducing information into the cytoplasm to **activate** the B lymphocyte once the sIgs bind to their particular epitopes. All of the immunoglobulin molecules on a particular B cell recognize and bind to the **same antigenic determinant** (**epitope**). Several types of B cells exist, but B-2 B cells and B-1 B cells are the most predominant forms.

(1) **B-2 B cells** are the "conventional" B cells *and will be referred to as "B cells"* in this textbook; they are the most numerous and are present throughout the body. They must interact with T cells to propagate (in the bone marrow) and to become activated; they recognize an immense number of **epitopes**; and they are able to switch isotypes (i.e., switch in the synthesis of antibody types) and establish **memory B cells**. They are considered to be firmly related to the adaptive immune system.

(2) **B-1 B cells** are much fewer in number than B cells and are usually limited to the gastrointestinal (GI) and respiratory systems. They do not possess CD40 molecules, very seldom require T-cell interaction, do not have to regenerate in the bone marrow but proliferate peripherally, and target **carbohydrates** rather than proteins. They very seldom switch isotypes and do not establish memory B-1 B cells. They are a cross over between the innate and adaptive immune systems.

c. **CD40** molecules are present on the plasmalemmae of B cells. They interact with CD40 receptors on T_H2 cells, causing release of cytokines that facilitate proliferation and transformation of B cells into B memory and plasma cells and inhibit T_H1 cell proliferation. The specific cytokines that are released by T helper cells depend on the **invading pathogen**.

(1) IL-4 and IL-5 are released by T helper cells in response to parasitic worms causing B cells to switch to IgE formation.

(2) IL-6 and IFN-γ are released by T helper cells in response to bacteria and viruses in the connective tissue, causing B cells to switch to IgG formation.

(3) Transforming growth factor β (TGF-β) is released by T helper cells in response to the presence of bacteria and viruses on mucosal surfaces causing B cells to switch to IgA formation.

d. B lymphocytes can present epitopes complexed with class II human leukocyte antigen (class II MHC) to T_H1 cells; therefore, they are considered to be **APCs**.

e. When activated, B lymphocytes release **IL-12** to induce T_H1 cell formation and NK cell activation. During a humoral immune response to an antigenic challenge, B lymphocytes proliferate and differentiate to form **plasma cells** and **B memory cells** (Fig. 10.1A).

2. Plasma cells

lack surface antibody and actively synthesize and secrete **antibodies specific against the challenging antigen**.

3. B memory cells

are **long-lived committed immunocompetent cells** that are formed during proliferation in response to an antigenic challenge. They do not react against the antigen but remain in the circulation or in specific regions of the lymphoid system. By increasing the size of the original clone, they **provide** a faster and greater **secondary response** (**anamnestic response**) against a future challenge by the same antigen.

4. Two groups of B cells exist in the spleen: the more populous follicular B cells and fewer marginal zone (MZ) B cells.
   a. **Follicular B cells** are more populous and are located in the primary and secondary follicles of the spleen. They sport IgM, IgD, and CD21 surface markers, and they are T-cell-dependent for immune function. They are believed to be in the final stage of their maturation into fully functioning mature B cells.
   b. **MZ B cells** are fewer in number than follicular B cells and are located in the MZ of the spleen. They sport IgM, CD1, CD9, and CD21 on their plasmalemmae, and they are T-cell-independent for their immune functions. They react primarily to self-antigens and bacterial invasion.

CLINICAL CONSIDERATIONS

Common variable immunodeficiency is a disease of the young, developing in patients who are between 10 and 20 years of age. Although these patients have normal B-cell populations, they do not manufacture enough immunoglobulins, with the consequence of recurrent respiratory infections and the development of autoimmune disorders such as rheumatoid arthritis, thyroiditis, and Addison disease. Affected individuals frequently suffer from GI disorders, such as diarrhea and insufficient absorption of nutrients from the alimentary canal.

Hodgkin disease, a malignant **neoplastic transformation of lymphocytes**, occurs mostly in young men and is characterized by the presence of **Reed–Sternberg cells**, which are giant cells with two large, vacuolated nuclei, each with a dense nucleolus. Signs and symptoms of Hodgkin disease include painless progressive **enlargement of the lymph nodes**, **spleen**, and **liver**; anemia; fever; weakness; anorexia; and weight loss.

D. **NK cells belong to a category of *null cells*, a small group of peripheral blood lymphocytes that *lack the surface determinants* that are characteristic of T and B lymphocytes.** However, they do possess two specific receptors, **killer activation receptors** that respond to stress molecules and **killer inhibition receptors** that respond to **MHC class I molecules**. It is these receptors that aid them in the recognition of virally altered cells and tumor cells that have to be forced into apoptosis.
   1. As soon as they are formed, NK cells are immunocompetent without having to enter the thymic environment. Not only are NK cells not MHC restricted, but they also exhibit an apparently **nonspecific cytotoxicity** against tumor cells and virus-infected cells. The mechanism by which NK cells recognize these target cells is not yet understood.
   2. NK cells can also kill specific target cells that have antibodies bound to their surface antigens in a process known as **antibody-dependent cell-mediated cytotoxicity** (**ADCC**); macrophages, neutrophils, and eosinophils also exhibit ADCC. They use **perforins** and **granzymes** to drive the virally altered cells or tumor cells into **apoptosis**.

CLINICAL CONSIDERATIONS

Many cancer cells protect themselves from destruction by using proteins and sugars on their surfaces that have the ability to block cells of the immune system from recognizing the cancer cell as an altered cell that has to be killed. Cells of the immune system possess on their plasma membranes a family of at least 14 proteins, known as **Siglecs**, which recognize and bind to **sialic acid**, thereby ignoring the malignant cell. Recently, NK cells were found to possess the protein Siglec-7 on their plasma membranes, and, when they encounter cancer cells with sialic acid residues, the NK cells ignore the malignant cells. However, if the cancer cells were treated, in vitro, with an antibody to which the enzyme sialidase was coupled, sialidase removed the sialic acid residue, the NK cells became activated, and they forced the cancer cells into apoptosis. Current investigations are under way to find a method whereby the same reaction can be effective **in vivo**.

E. ***Macrophages* are not only phagocytes, but also function both as *APCs* and as *cytotoxic effector cells* in ADCC.**
   1. They possess receptors for the Fc portion of antibodies, for certain complements, and for carbohydrates that are not normal components of cell membranes. When macrophages bind to these substances they become activated to phagocytose the structures bearing them.

2. When acting as APCs, macrophages phagocytose antigens, fragment them into small antigenic components, known as **epitopes**, and present them to T cells.
3. Macrophages produce and release **IL-1**, which helps activate T_H cells and self-activate macrophages. Moreover, they produce **TNF-α**, which also self-activates macrophages and induces the release of **IL-12**; in conjunction with **interferon-γ** (**IFN-γ**) they facilitate the killing of endocytosed bacteria. In addition, macrophages secrete **prostaglandin E_2** (**PGE_2**), which decreases certain immune responses; **IL-6**, which activates T cells and stimulates B cells to differentiate into plasma cells; **IL-12**, which activates T_H1 cells to proliferate and activates NK cells; **IL-18**, which acts on T_H1 cells to produce IFN-γ and also enhances NK cell activity; and **IL-23**, which decreases the motility of $CD8^+$ T cells. Also note that **IL-1**, **IL-6**, and **TNF-γ** act together to induce an **inflammatory process**.

CLINICAL CONSIDERATIONS

Recent studies have demonstrated an interesting new role for macrophages. Macrophages have long been known to reside among cardiac muscle cells, especially among cells of the atrioventricular node (AV node). Cardiac muscle cells as well as cells of the AV node undergo rhythmic contraction, and this ability, especially of the AV cells, is essential for normal contraction of the heart. These cells must be able to depolarize and repolarize their cell membranes, and, to be able to do that, they require a constant availability of ions. Macrophages are now thought to form gap junctions with cardiomyocytes and AV cells through which they can transfer the requisite ions, so that these cells always have enough ions to depolarize their plasmalemma, thereby undergoing contraction.

III. ANTIGEN PRESENTATION AND THE ROLE OF MHC MOLECULES

A. MHC molecules

1. MHC molecules are integral membrane proteins coded by large genetic complexes with many loci. The two main classes of MHCs are **class I major histocompatibility molecules** (**MHC I**), which are expressed by nearly all **nucleated cells**, and **class II histocompatibility molecules** (**MHC II**), which are expressed by the various cells that function as **APCs**.
2. In humans, the MHC is referred to as the **HLA complex**. Therefore, MHC I is class I HLA, and MHC II is class II HLA. As described below, MHC I molecules bind epitopes derived from **endogenous proteins**, whereas MHC II molecules bind epitopes derived from **exogenous proteins**. Both types of MHC molecules present their epitopes to T cells.

B. Immunogens are molecules that are capable of *inducing an immune response*.

All immunogens are **antigens**, that is, molecules whose **epitopes** can react with an **antibody** or a **TCR**. Most, but not all, antigens are immunogens.

1. **Exogenous immunogens** are derived from proteins that were endocytosed or phagocytosed by APCs and degraded intracellularly, yielding antigenic peptides containing an epitope that enters the *trans*-Golgi network (TGN).
2. In the TGN, the complex is sorted into specialized antigenic peptides (containing an epitope) that associate with **class II HLA molecules** (MHC II molecules).
   a. These epitopes are relatively long, composed of 13 to 25 amino acids.
   b. Class II HLA molecules are synthesized on the rough endoplasmic reticulum (RER) and are loaded *within* the RER cisternae with a protein known as **CLIP** (**cl**ass II–associated **i**nvariant **p**rotein).
   c. The class II HLA–CLIP complex enters the Golgi apparatus, where it is delivered to MIIC vesicles (**MHC class II compartment vesicles**, which already contain epitopes derived from exogenous immunogens), where the CLIP is exchanged for the epitope.
   d. The epitope–class II HLA complexes are transported to and displayed on the cell surface, where they are **presented** to T cells.

3. **Endogenous immunogens** are derived from proteins that were produced **within** host cells (these may be **viral proteins** synthesized in virus-infected cells or **tumor proteins** synthesized in cancerous cells).
   a. **Class I HLA molecules** (MHC I molecules), synthesized on the RER surface, enter the RER cisternae.
   b. Endogenous immunogens are degraded by organelles of the host cells, known as **proteasomes**, into short polypeptide fragments. These fragments are antigenic peptides (8–12 amino acids in length) known as **epitopes** which are transported by **TAP1** and **TAP2** (**tra**nsporter **p**roteins 1 and 2) into the RER cisternae.
   c. Within the RER cisternae, the epitopes derived from endogenous immunogens are loaded on the **class I HLA**. The peptide–class I HLA complexes are transported to the Golgi complex for sorting and eventual delivery within clathrin-coated vesicles to the cell surface, where they are presented to T cells.

C. MHC (HLA) restriction—T lymphocytes. **Each subtype of T lymphocytes (except T memory cells) recognizes only epitopes that are associated with either MHC I or MHC II (class I or class II HLA) molecules as follows:**

1. T_H1 and T_H2 cells ($CD4^+$ cells) recognize MHC II (class II HLA) molecules.
2. Cytotoxic T cells ($CD8^+$ cells) recognize MHC I (class I HLA) molecules.
3. T memory cells (CD45R0 cells) recognize both MHC I and MHC II (class I and class II HLA) molecules.

IV. IMMUNOGLOBULINS

Immunoglobulins are glycoproteins that are synthesized and secreted by **plasma cells**. They constitute the active agents of the humoral immune response and have **specific antibody activity** against one antigen or a few very closely related antigens. Immunoglobulins bind antigens to form antigen–antibody complexes, which are cleared from the body by various means, some of which involve the **complement system**, whereas others involve **eosinophils**.

A. Structure

1. **Immunoglobulins** are composed of monomers containing two **heavy chains** and two **light chains**.
2. Each immunoglobulin possesses a **constant region** that is identical in all immunoglobulin molecules of the same isotype as well as a **variable region** that differs in the antibody molecules that recognize different antigens. Thus, the **variable regions determine the specificity** of an antibody molecule (i.e., its ability to bind to a particular antigenic determinant). Large antigens may have multiple antigenic determinants, which induce production of antibodies with different specificities.

B. Immunoglobulin classes (Table 10.4)

1. Human serum contains five classes (**isotypes**) of immunoglobulins, which differ in the amino acid composition of their **heavy-chain constant regions**.
2. The different isotypes exhibit functional differences.
   a. **IgA** is secretory immunoglobulin that is released, in the form of dimers, into tears, bile, saliva, milk, and as part of the nasal discharge to protect the body (and the nursing infant) from pathogenic microorganisms and invading antigens. It is protected from digestive enzymes by its **secretory component** synthesized by epithelial cells and hepatocytes.
   b. **IgD** and **IgE** are reaginic antibodies; IgE binds to IgE receptors of **mast cells** and **basophils** and, when cross-bound by antigens, prompts the release of pharmacologic agents from these cells to initiate an **immediate hypersensitivity response**. IgD binds to B-cell plasma membranes and permits these cells to recognize antigens and thus initiate a response against antigenic challenges by prompting B cells to differentiate into antibody-secreting **plasma cells**.
   c. **IgG**, the most abundant serum immunoglobulin, can cross the placental barrier to shield the fetus—a process known as **passive immunity**. It attaches to antigenic sites on invading

table 10.4 Ig Isotypes and Their Characteristics

Class	Type of Ig	Cytokines Required for Isotype Switch	Fraction of All Igs (%) and Half-life (Days) in Serum	Binding to Cells	Biologic Characteristics
IgA	Secretory antibody	Transforming growth factor-β	10%–15% 6 days	Forms temporary attachment to epithelial cells as it is being secreted	Secreted as dimers into saliva, tears, bile, lumen of gut, and milk (providing passive immunity for infants); dimers protected by their secretory component. IgA provides protection against pathogens and invading antigens
IgD	Reaginic antibody		0.2% 3–8 days	B-cell plasmalemma	Allows B cells to recognize antigens and elicits an immune response by inducing B-cell transformation into plasma cells
IgE	Reaginic antibody	IL-4 and IL-5	Much less than 1% 2–5 days	Plasmalemmae of mast cells and basophils	Antigenic binding to IgE located on mast cell and basophil plasma membranes, induces these cells to release their pharmacologic agents inducing an instantaneous hypersensitivity response
IgG	Serum immunoglobulin	IFN-γ, IL-4, and IL-6	65%–75% 23 days	Neutrophils and macrophages	IgG can penetrate the placental barrier, thereby providing the fetus with passive immunity. IgG binds to antigenic sites on invading pathogens, opsonizing them facilitating phagocytosis by macrophages and neutrophils. IgG induces NK cells, thus initiating ADCC
IgM	First to be formed in immune response		8%–10% 5–10 days	IgM is a pentamer; however, its monomeric form binds to B cells	Pentameric IgM activates the complement system. The principal place of formation of IgM is the spleen

ADCC, antibody-dependent cell-mediated cytotoxicity; IFN, interferon; Ig, immunoglobulin; IL, interleukin; NK, natural killer.

microorganisms, thus **opsonizing** these pathogens, making them available for phagocytosis by macrophages and neutrophils. These antibodies activate NK cells, thus initiating **ADCC**.

d. IgM forms pentamers and is the first isotype to be formed in an immune response. It activates the **complement system**. Its monomeric form binds to the B-cell plasma membrane.

CLINICAL CONSIDERATIONS

Pharmaceutical companies manufacture human antibodies for clinical purposes by inducing hamster ovary cells to synthesize them. This process is relatively expensive, so some smaller pharmaceutical companies have started using plants, mostly tobacco plants, for the same purpose. They place the gene for the particular antibody into attenuated viruses and infect the leaves of the plant with the altered virus, and the tobacco plant manufactures the human antibody, which can be harvested within a short period of time. These antibodies, referred to as **plantibodies**, are in clinical trials and are expected to be available in a few years for clinical use.

V. DIFFUSE LYMPHOID TISSUE

Diffuse lymphoid tissue, collectively called **mucosa-associated lymphoid tissue** (**MALT**), is considered to be a secondary lymphoid tissue. It is especially prominent in the mucosae of the GI and respiratory systems and is organized as nonencapsulated clusters of lymphoid cells or as lymphoid (lymphatic) nodules.

A. MALT consists of two major types, *bronchus-associated lymphoid tissue* and *gut-associated lymphoid tissue* (*GALT*). Both types possess lymphoid nodules that are isolated from one another, except in the case of **Peyer patches**, which are aggregates of lymphoid nodules found in the **ileum**.

B. Lymphoid (lymphatic) nodules are transitory dense spherical *accumulations of lymphocytes* (mostly B cells) in which the dark, peripheral region of nodules (*corona*) is composed mainly of small, newly formed lymphocytes. Lymphoid nodules of the GALT are isolated from the lumina of their respective tracts by **microfold (M) cells**, which transfer antigens from the lumen and present them (**without** processing them into epitopes) to lymphocytes and macrophages lying in deep invaginations of their basal cell surfaces. From here, an appropriate immune response is mounted by lymphoid tissue in the connective tissue, known as the **lamina propria**.

1. **Secondary nodules**, formed in response to an antigenic challenge, have a lightly staining central area called the **germinal center**, which is composed of B lymphocytes (**centroblasts** and **centrocytes**). A darker region, known as the **mantle (corona)**, is composed of resting B cells that are being displaced from the germinal center by the newly formed B cells. In addition to centroblasts and centrocytes, the germinal center houses B memory cells, plasma cells, migrating dendritic cells, follicular dendritic cells, macrophages, and reticular cells.
   a. **Centroblasts** do not display surface immunoglobulins (sIgs), whereas centrocytes have expressed sIgs.
   b. All **centrocytes** that express sIgs against self are forced into apoptosis, whereas centrocytes that do not express sIgs against self become **B memory cells** or **plasma cells**.
   c. **Migrating dendritic cells** are derived from the bone marrow and are located in various regions of the body. When they encounter an antigen, they travel to a nearby lymphoid nodule or lymph node to precipitate an immune reaction.
   d. **Follicular dendritic cells** are resident cells of lymph nodes or lymphoid nodules and challenge the sIgs of newly formed centrocytes and force those centrocytes that do not possess the proper sIgs into apoptosis. **Macrophages** phagocytose the remnants of apoptotic cells.
   e. **Reticular cells** are fibroblast-like cells that manufacture reticular fibers (type III collagen) to form the supporting skeleton of the lymphoid nodule and lymph node.
2. **Primary nodules** lack germinal centers and are composed of resting B memory cells, plasma cells, migrating dendritic cells, follicular dendritic cells, macrophages, and reticular cells.

VI. LYMPHOID ORGANS

A. Lymph nodes

1. **Overview**
   a. A lymph node is a small, encapsulated ovoid to kidney-shaped structure with a connective tissue capsule that sends **trabeculae** into the substance of the node (Figs. 10.2 and 10.3). The **convex** surface of a lymph node receives afferent lymphatic vessels, whereas the **concave** surface (the **hilum**) is the site where arterioles enter and venules and efferent lymphatic vessels exit. The connective tissue element of lymph nodes, known as the **stroma**, is composed of **stromal cells** and a supportive framework rich in **reticular fibers**.
   b. **Function.** Lymph nodes filter lymph, maintain and produce T and B cells, and possess memory cells (especially T memory cells). Antigens delivered to lymph nodes by APCs are recognized by T cells, and an immune response is initiated. Additionally, some of the **stromal cells** and some of the **dendritic cells** of lymph nodes express the transcription factor **AIRE** that selectively induces anti–self-T cells that escaped destruction in the thymus to go into apoptosis.
2. **Structure.** Lymph nodes are divided into three regions, the outermost **cortex**, the middle **paracortex**, and the innermost **medulla** (Figs. 10.2 and 10.3). Stromal cells of these regions release a variety of **chemotactic chemokines lymphocytes (CCLs)** that attract lymphocytes. Depending on the CCL released, B cells or T cells are attracted to a particular region of the lymph node. In order to attract both B cells and T cells, CCLs are conveyed to the luminal endothelial cell membranes of postcapillary venules, the region where lymphocytes leave the circulatory system to enter the substance of the lymph node. Once in the lymph node stroma, both B cells and T cells are segregated within the cortex of the lymph node by the CCLs to which each responds.
   a. The **cortex** of lymph nodes lies deep to the capsule and is separated from it by the **subcapsular sinus**. The cortex is incompletely subdivided into compartments by connective

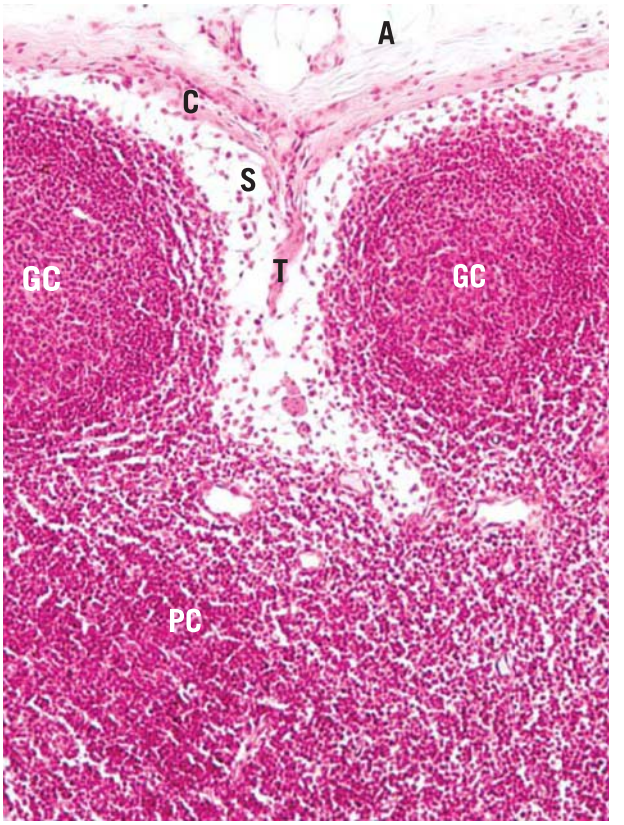


FIGURE 10.2. This photomicrograph of a human lymph node demonstrates that the capsule (C) of the node is surrounded by adipose tissue (A). The capsule sends trabeculae (T) into the substance of the node. Note the presence of the subcapsular and paratrabecular sinusoids (S) as well as the germinal centers (GC) of the lymphoid nodules. The paracortex (PC) is evident between the cortex and the medulla (×132).

tissue septa (trabeculae) derived from the capsule and contains lymphoid nodules and sinusoids.

(1) **Lymphoid nodules** are composed mainly of B cells but also of some T cells, follicular dendritic cells, macrophages, and reticular cells. Those that possess a germinal center are known as secondary lymphoid nodules.

(2) **Sinusoids** are endothelium-lined lymphatic spaces that extend along the capsule and trabeculae and are known as **subcapsular** and **cortical sinusoids**, respectively.

b. The **paracortex** of the lymph node, located between the cortex and the medulla, is composed of a nonnodular arrangement of **mostly T lymphocytes** (the thymus-dependent area of the lymph node) and **dendritic cells**. It is the region where circulating lymphocytes gain access to lymph nodes via **postcapillary** (**high endothelial**) **venules** (**HEVs**).

c. The **medulla** of a lymph node lies deep to the paracortex and cortex, except at the region of the hilum. It is composed of medullary sinusoids and medullary cords (Fig. 10.3).

(1) **Medullary sinusoids** are endothelium-lined spaces supported by reticular fibers and reticular cells. They receive lymph from the cortical sinuses and frequently contain macrophages. **Medullary cords** are composed of lymphocytes and plasma cells.

B. The thymus is a primary lymphoid organ.

1. Overview

a. The thymus, a bilobed structure located in the superior mediastinum, is derived from **endoderm** (**epithelial reticular cells**) and from **mesoderm** (**lymphocytes** [**thymocytes**]). A connective tissue **capsule** surrounds the thymus and **septa** derived from it divide the parenchyma

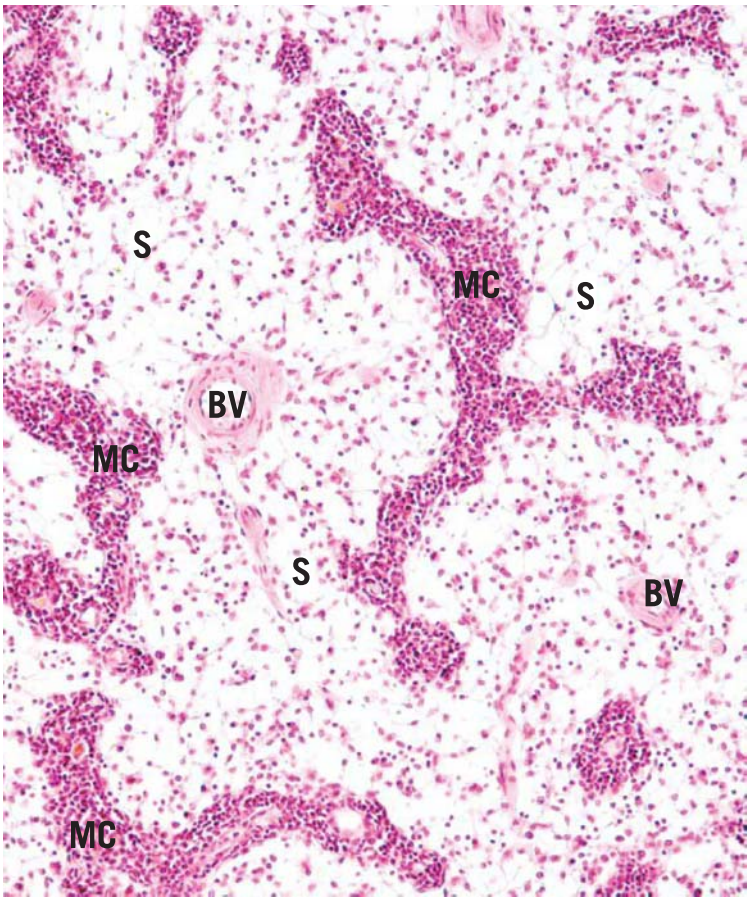


FIGURE 10.3. This photomicrograph of the medulla of a human lymph node displays the presence of medullary cords (MC), blood vessels (BV) as well as medullary sinusoids (S) (×132).

into incomplete lobules, each of which contains a **cortical** and **medullary region** (Figs. 10.4 and 10.5) but without the presence of lymphoid nodules. The development of the epithelial reticular cells of the thymus (especially in the medulla) is dependent on the formation and release of **lymphotoxins**, members of the TNF family of cytokines. In the absence of these proteins, the thymus does not develop or function properly. The thymus begins to **involute** (i.e., degenerate) near the time of puberty.

2. Structure

a. The **thymic cortex** is supplied by arterioles in the septa; these arterioles provide capillary loops that enter the substance of the cortex. The cortex is the region in which **T-cell maturation** occurs.

(1) Epithelial reticular cells (Fig. 10.5)

(a) The six types of epithelial reticular cells (Table 10.5) are pale cells (derived, during embryogenesis, from the third pharyngeal pouches) and have a large ovoid lightly staining nucleus that often displays a nucleolus.

(b) They possess **long processes** that surround the thymic cortex, isolating it from both the connective tissue septa and the medulla. These processes, which are filled with bundles of **tonofilaments**, form desmosomal contacts with each other. They manufacture **thymopoietin**, a protein that induces CD90 Thy-1 expression on thymocytes and perhaps thereby the activation of T cells, and **thymic stromal lymphopoietin (TSLP)** which activates certain dendritic cells of the thymus to prevent the destruction of some self-reactive T cells and transform them into highly reactive natural T reg cells. They also manufacture **AIRE**, the autoimmune regulator transcription factor discussed above (see Section II B).

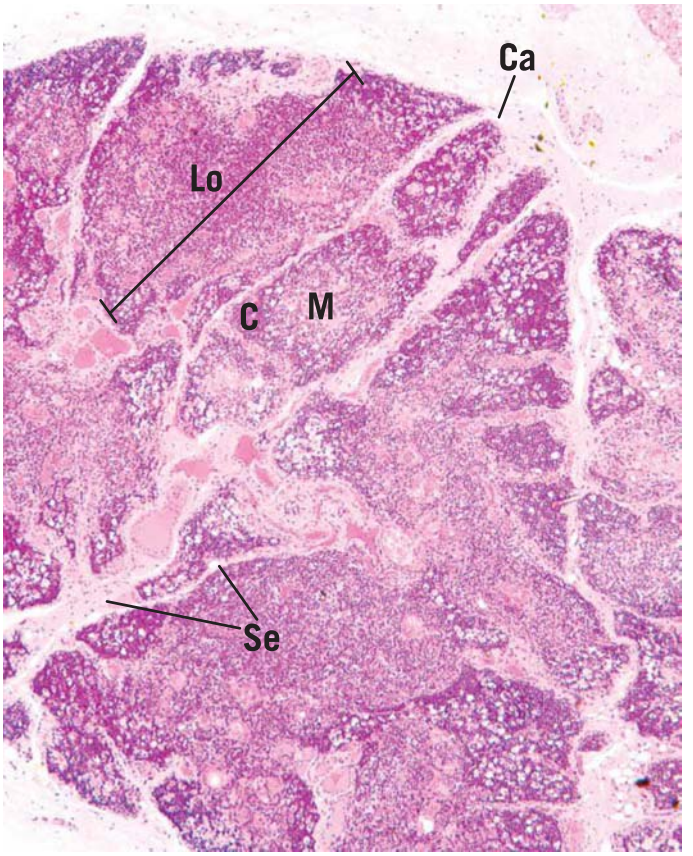


FIGURE 10.4. This survey photomicrograph of the monkey thymus displays its connective tissue capsule (Ca) as well the connective tissue septa (Se) that divides this organ into lobules (Lo). Each lobe has a cortex (C) and a medulla (M), where the medulla is continuous between adjacent lobules (×56).

(2) **Thymocytes**

(a) **Thymocyte** plasmalemma possesses Notch-1 receptors that permit these cells to respond to cytokines released by epithelial reticular cells to become T cells. Once committed to the T-cell lineage, they are known as **immature T lymphocytes** and are noted to be present within the thymic cortex in different stages of differentiation.

(b) Thymocytes are surrounded by processes of epithelial reticular cells, which help segregate thymocytes from antigens during their maturation. These cells migrate toward the medulla as they mature.

(c) Most T cells die in the cortex, and the dead cells are phagocytosed by macrophages. Surviving T cells are naïve. They leave the thymus and are distributed to secondary lymphoid organs by the vascular system.

(3) **Blood–thymus barrier**

(a) The blood–thymus barrier exists in the **cortex only**, making it an immunologically protected region, ensuring that antigens escaping from the bloodstream do not reach developing T cells in the thymic cortex.

(b) This barrier consists of the following layers: **endothelium** of the thymic capillaries and the associated basal lamina, **perivascular connective tissue** and **cells** (e.g., pericytes and macrophages), and **epithelial reticular cells** and their basal laminae.

b. **Thymic medulla**

(1) The thymic medulla is continuous between adjacent lobules and contains large numbers of **epithelial reticular cells** and **mature T cells**, which are loosely packed, causing the medulla to stain lighter than the cortex (Fig. 10.5).

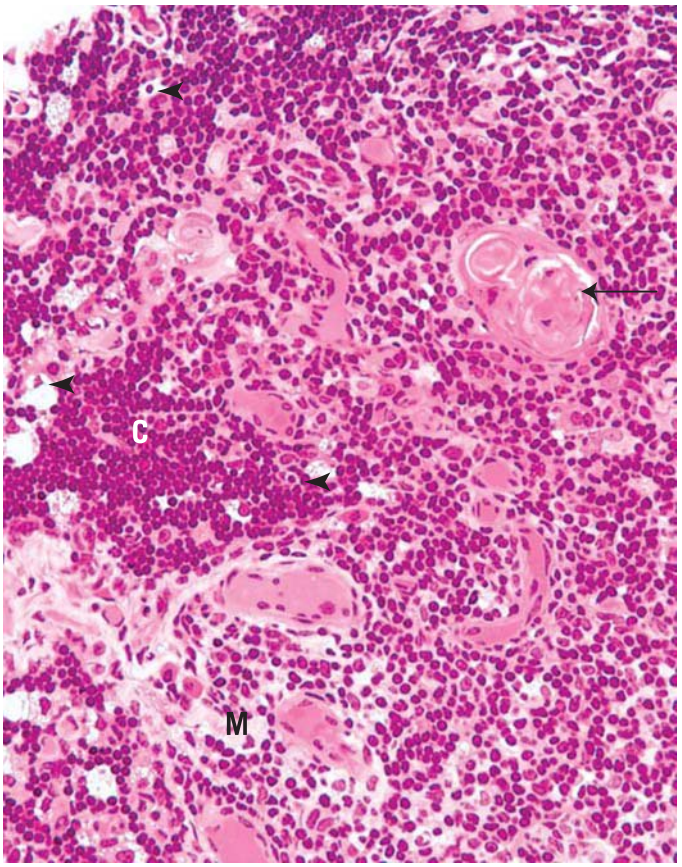


FIGURE 10.5. This low-power photomicrograph of the monkey thymus displays the dense cortex (C) and the lighter medulla (M). Note the numerous epithelial reticular cells (*arrowheads*) that are quite evident in the cortex as well as the thymic (Hassall) corpuscles (*arrow*) in the medulla (×132).

table 10.5 Reticular Epithelial Cells of the Thymus

Type	Location	Function
Cortex		
I	Junction of the capsule and the cortex as well as surrounding the trabeculae that partially separates thymic lobules from each other	Forms a barrier between the thymic parenchyma and the rest of the body; it also assists in the formation of the blood–thymus barrier by surrounding blood vessels in the thymic cortex
II	Stellate-shaped cells in the cortex where the processes of adjacent cells form desmosomes with each other	The processes surround and form compartments isolating maturing T cells. They express MHC I and MHC II and self-antigen molecules and present them to maturing T cells
III	On the cortical aspect of the corticomedullary junction	They form the boundary between the cortex and the medulla. They express MHC I and MHC II and self-antigen molecules and present them to maturing T cells
Medulla		
IV	On the medullary aspect of the corticomedullary junction	They and type III cells isolate the cortex from the medulla
V	Throughout the medulla	Form the cytoarchitectural framework of the medulla and form compartments for T cells
VI	Medulla	Form Hassall corpuscles, which are believed to be responsible for deletion of T-cell clones that would recognize and attack self-proteins. Manufacture and release TSLP that aids in the formation of natural T reg cells

MHC, major histocompatibility complex; TSLP, thymic stromal lymphopoietin.

(2) The medulla of the thymus also contains whorl-like accretions of epithelial reticular cells called **Hassall corpuscles** (**thymic corpuscles**). These structures display various stages of keratinization and increase in number with age. Their function is unknown, although it has been shown that these epithelial reticular cells manufacture **TSLP**, a cytokine that facilitates dendritic cell maturation which, in turn, elicit the transformation of naïve T cells into natural T reg cells.
(3) Mature T cells exit the thymus via venules and efferent lymphatic vessels from the thymic medulla. The T cells then migrate to secondary lymphoid structures.
(4) Hormones acting on the thymus
  (a) **Thyroxin** encourages thymulin production by epithelial reticular cells.
  (b) **Adrenocorticosteroids** depress T-cell formation in the thymus.

CLINICAL CONSIDERATIONS

DiGeorge syndrome, also called **congenital thymic aplasia**, is characterized by the congenital absence of the thymus and parathyroid glands, resulting from abnormal development of the third and fourth pharyngeal pouches. This syndrome is associated with **abnormal cell-mediated immunity** but relatively normal humoral immunity; however, it usually results in **death** from **tetany** or uncontrollable **infection.**

C. Spleen

1. Overview

a. A simple squamous epithelium (peritoneum) covers the dense irregular collagenous connective tissue **capsule** of the spleen, which sends **trabeculae** into the substance of the spleen to form a supportive framework (Fig. 10.6). Major vessels of the spleen enter and leave this organ at a depression known as the hilum. The spleen filters blood, phagocytoses damaged and aged erythrocytes, and is a site of proliferation of B and T lymphocytes and the production of antibodies by plasma cells. In some animals, such as the dog, but not in humans, it stores red blood cells.

b. The spleen differs from both the thymus and lymph nodes in that it **lacks a cortex and medulla** and instead is divided into **red pulp** and **white pulp**, where the latter contains lymphoid elements. These two regions are separated from each other by the **MZ** (Fig. 10.6). It further differs from lymph nodes because it has no **afferent lymphatic vessels**.

2. Vascularization of the spleen

is derived from the **splenic artery**, which enters the hilum and gives rise to trabecular arteries.

a. **Trabecular arteries** leave the trabeculae, become invested by a **periarterial lymphatic sheath** (**PALS**), and are known as **central arteries** which branch but maintain their lymphatic sheath until they leave the white pulp to form several straight **penicillar arteries** which enter the red pulp where they display three regions: **pulp arterioles, macrophage-sheathed arterioles,** and **terminal arterial capillaries**. These capillaries either drain directly into the splenic sinusoids (**closed circulation**) or terminate as open-ended vessels within the splenic cords of the red pulp (**open circulation**).

b. **Splenic sinusoids** are drained by pulp veins, which are tributaries of the trabecular veins; these in turn drain into the splenic vein, which exits the spleen at the hilum.

3. Structure

a. **White pulp of the spleen** includes **all** of the organ's lymphoid tissue (diffuse and nodular), such as **lymphoid nodules** (mostly B cells) and **PALS** (mostly T cells) around the central arteries. It also contains macrophages and other APCs.

b. The **marginal zone (MZ) of the spleen** is a **sinusoidal region** between the red and white pulps at the periphery of the white pulp (Fig. 10.6), which receives blood from capillary loops derived from the central artery and thus is the **first site where blood contacts the splenic parenchyma**.
(1) **The MZ** is richly supplied by avidly phagocytic macrophages and other APCs. The two types of macrophages in the MZ are the **MZ macrophages** and **MZ metallophilic macrophages**.
  (a) **MZ macrophages** express molecules on their surfaces that recognize pathogens such as bacteria, viruses, and yeasts.

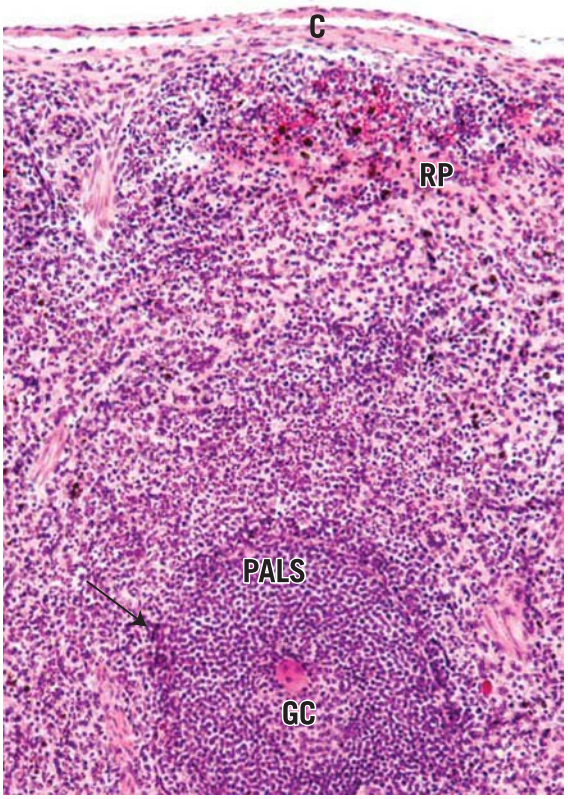


FIGURE 10.6. This low-power photomicrograph displays the smooth capsule (C) of a human spleen. Observe that the spleen is not divided into a cortex and a medulla; instead, it has red pulp (RP) and white pulp. Note the presence of a lymphoid nodule with a germinal center (GC) composed of B lymphocytes. The lymphoid nodule is invested by the T-cell–rich region of the spleen, known as the periarterial lymphatic sheath (PALS). The *arrow* points to the marginal zone located between the white pulp and the RP (×132).

(b) **MZ metallophilic macrophages** express molecules that bind to cell-bound oligosaccharide ligands; these macrophages also interact with **MZ B cells** inducing them to migrate to the white pulp of the spleen and present blood-borne antigens to T cells.

(2) Circulating T and B lymphocytes enter the spleen at the MZ before becoming segregated to their specific locations within the organ and where **interdigitating dendritic cells** are able to display their MHC–epitope complex for recognition by T cells.

(3) Stromal cells of the MZ release a variety of **chemotactic chemokines for lymphocytes** (**CCLs**) that attract lymphocytes. Depending on the CCL released, B cells or T cells are attracted to a particular region of the spleen. In order to attract both B cells and T cells to the MZ, CCLs are conveyed to the luminal endothelial cell membranes of MZ sinusoids. Once in the spleen parenchyma, both B cells and T cells are segregated within the white pulp of the spleen by those CCLs to which each responds.

c. **Red pulp of the spleen** (Fig. 10.6) is composed of an interconnected network of sinusoids supported by a loose type of reticular tissue (**splenic cords**).

(1) **Sinusoids** are lined by long fusiform endothelial cells called Stave cells, separated by relatively large blood-containing intercellular spaces, and have a discontinuous basal lamina underlying the endothelium and circumferentially arranged ribs of reticular fibrils.

(2) **Splenic cords** (**cords of Billroth**) contain plasma cells, stellate reticular cells, blood cells, and macrophages enmeshed within the spaces of the reticular fiber network. Processes of the macrophages enter the lumina of the sinusoids through the spaces between the endothelial cells.

D. Tonsils are aggregates of lymphoid tissue, which sometimes lack a capsule. All tonsils are in the upper section of the digestive tract, lying beneath but in contact with the epithelium. B and T cells in the three sets of tonsils are localized in different regions of any particular tonsil. The mechanism of distribution is similar to that which occurs in lymph nodes and the spleen and depends on the various **chemokines for lymphocytes** (**CCLs**) secreted by stromal cells. Tonsils assist in combating antigens entering via the nasal and oral epithelia.

1. **Palatine tonsils** possess crypts, deep invaginations of the nonkeratinized stratified squamous epithelium covering of the tonsils, frequently containing debris. They have primary and secondary (with germinal centers) lymphoid nodules and are separated from subjacent structures by a connective tissue capsule.
2. The **pharyngeal tonsil**, located in the posterior wall of the nasopharynx is covered by a pseudostratified ciliated columnar epithelium. Instead of crypts, it has longitudinal pleats (infoldings). The pharyngeal tonsil possesses primary and secondary (with germinal centers) lymphoid nodules.
3. The **lingual tonsil** is located on the dorsum of the posterior third of the tongue and is covered by a stratified squamous nonkeratinized epithelium. It possesses wide **crypts**, which frequently contain cellular debris. Ducts of the posterior mucous glands of the tongue often open into the base of these crypts. Similar to the other two tonsils, the lingual tonsil also possesses primary and secondary (with germinal centers) lymphoid nodules.

Review Test

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or completions of the statement. Select the ONE lettered answer that is BEST in each case.

1. A patient who was given penicillin had an adverse reaction to the antibiotic. Although the reaction was due to the actions of mast cells, the response occurred because mast cells have IgE receptors in their cell membranes. Which cells produce the IgE on the plasma cell's surface?

(A) T memory cells
(B) B memory cells
(C) T helper cells
(D) Plasma cells
(E) T cytotoxic cells

2. A pregnant woman who is in her 22nd week of pregnancy is seen by her gynecologist/obstetrician for her regular prenatal care visit. The physician sees that the patient, whose blood pressure has been normal throughout her pregnancy, has a drastically elevated blood pressure. The physician suspects the possibility of preeclampsia. Which TLR is associated with preeclampsia?

(A) TLR1
(B) TLR2
(C) TLR3
(D) TLR4
(E) TLR5

3. A patient getting his annual physical tells his physician about an article he read about over 2 billion cells dying every day in each person. He asks her what happens to those dead cells. The physician tells him that each of those dead cells is eliminated by cells known as macrophages because the dead cells are marked for destruction by

(A) reaginic antibodies.
(B) natural antibodies.
(C) T lymphocytes.
(D) B lymphocytes.
(E) NK cells.

4. Patients with X-linked agammaglobulinemia display an absence of which cell type?

(A) T cells
(B) NK cells
(C) Mast cells
(D) Eosinophils
(E) B lymphocytes

5. HIV preferentially attacks which cell population?

(A) T helper cells
(B) T cytotoxic cells
(C) T memory cells
(D) NKTs
(E) Inducible T reg cells

6. Adoptive cell transfer therapy for treatment of lymphoblastic leukemia involves genetic engineering of which cell population?

(A) NK cells
(B) T cells
(C) Mast cells
(D) Eosinophils
(E) B cells

7. A young male patient's lymph node biopsy displays the presence of Reed–Sternberg cells. He also presents with painless progressive enlargement of the lymph nodes, spleen, and liver; anemia; fever; weakness; anorexia; and weight loss. These findings are indicative of which condition?

(A) AIDS
(B) Multiple myeloma
(C) Common variable immunodeficiency
(D) Kaposi sarcoma
(E) Hodgkin disease

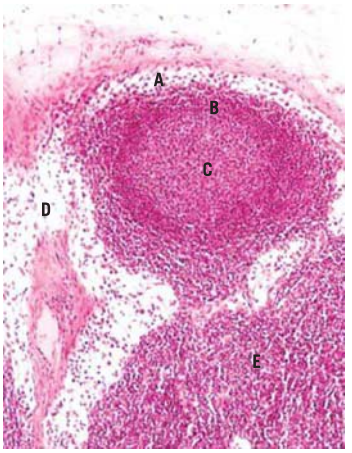
8. Which of the following statements concerning IFN-γ is true?

(A) It is produced by T memory cells.
(B) It is produced by T reg cells.
(C) It activates macrophages.
(D) It inhibits macrophages.
(E) It induces viral proliferation.

9. Which of the following statements about IgG is true?

(A) It is located in the serum and on the membrane of B cells.
(B) It can cross the placental barrier.
(C) It is involved in allergic reactions.
(D) It exists as a pentamer.
(E) It binds to antigens on the body surface and in the lumen of the GI tract.

The following question is based on the accompanying photomicrograph.



10. After their maturation in the thymus and release into the circulation, T lymphocytes migrate preferentially to which of the labeled sites on the photomicrograph?

(A) A
(B) B
(C) C
(D) D
(E) E

Answers and Explanations

1. **D.** Individuals allergic to penicillin produce IgE antibodies. The cells that manufacture IgE are plasma cells. After an antigenic challenge, proliferation and differentiation of B cells give rise to plasma cells and B memory cells.
2. **C.** A correlation between hypertension and TLR activity has been demonstrated, especially TLR3 in preeclampsia and TLR2 and TLR4 in angiotensin II–induced hypertension. Although the mechanism of TLR action is not understood, preganglionic neurons of the CNS may activate a sympathetic response that accounts for the increased state of hypertension.
3. **B.** These dead or dying cells display specific membrane molecules that are not present on the surfaces of healthy cells, and natural antibodies bind to these molecules. In this fashion natural antibodies mark these dead or dying cells for elimination by macrophages or dendritic cells.
4. **E.** In the case of this patient who suffers from X-linked agammaglobulinemia, B lymphocytes do not develop, resulting in scarcity of plasma cells and consequently lack of immunoglobulin production.
5. **A.** HIV, which preferentially invades T helper cells, causes a severe depression in their number, thus suppressing both cell-mediated and humoral immune responses.
6. **B.** A relatively new method for treating advanced acute lymphoblastic anemia (ALL), a disease in which lymphocytes (especially B cells) become malignant, involves what is known as adoptive cell transfer therapy, in which the patient's own T cells are removed and are genetically engineered to synthesize specific receptors that identify and bind to a particular cell surface antigen.
7. **E**. The presence of Reed–Sternberg cells, which are giant cells with two large, vacuolated nuclei, each with a dense nucleolus is indicative of Hodgkin disease. Signs and symptoms of this condition include painless progressive enlargement of the lymph nodes, spleen, and liver; anemia; fever; weakness; anorexia; and weight loss.
8. **C.** IFN-γ activates macrophages, NK cells, and T cytotoxic cells, enhancing their phagocytic or cytotoxic activity or both.
9. **B.** IgG is the most abundant immunoglobulin isotype in the serum. It can cross the placental barrier but does not bind to the B-cell plasma membrane. It exists as a monomer, functions to activate complement, and acts as an opsonin.
10. **E.** T lymphocytes are preferentially located in the paracortex of lymph nodes (labeled by the letter E).

chapter 11

Endocrine System

I. OVERVIEW—ENDOCRINE SYSTEM

Several **ductless glands**, **clusters of cells** within certain organs, and isolated individual **endocrine cells**, known as the **diffuse neuroendocrine system cells** (**DNES cells**), located in the epithelial lining of the respiratory and gastrointestinal systems constitute the **endocrine system**. Glands of the endocrine system include the **pituitary gland** (and a region of the brain known as the **hypothalamus**) as well as the **thyroid**, **parathyroid**, **adrenal**, and **pineal** glands. Additional components of the endocrine system, such as the islets of Langerhans, adipose tissue, female gonads, and male gonads, are discussed in the pertinent chapters. The endocrine system secretes hormones into nearby capillaries and interacts with the nervous system to modulate and control the body's metabolic activities.

II. HORMONES

Hormones are **chemical messengers** that are carried via the bloodstream to distant **target cells**. Hormones include low-molecular-weight **water-soluble** proteins, polypeptides, and amino acids (e.g., insulin, glucagon, follicle-stimulating hormone [FSH]) and **lipid-soluble** substances, principally the **steroid hormones** (e.g., progesterone, estradiol, and testosterone).

A. Water-soluble hormones **interact with specific cell surface receptors on target cells, which communicate a message that generates a biologic response by the cell.**
   1. **G protein–linked receptors** are used by some hormones (e.g., epinephrine, thyroid-stimulating hormone [TSH], serotonin). Binding of the hormone (**primary messenger**) to the G protein–linked receptor leads to production of a **second messenger** that evokes a target cell response.
   2. **Catalytic receptors** are used by insulin and growth hormone. Binding of the hormone to the catalytic receptor activates protein kinases that phosphorylate target proteins.

B. Lipid-soluble hormones **diffuse across the plasma membrane of target cells and bind to specific receptors in the cytosol or in the nucleus, forming hormone–receptor complexes that regulate transcription of deoxyribonucleic acid (DNA).**

CLINICAL CONSIDERATIONS

Mutations that alter the structure of G protein–linked receptors may interfere with the ability of the hormone to produce the desired result. An example of such disease-causing mutations is congenital hyperthyroidism. Mutations in the ***thyroid-stimulating hormone receptor* (*TSHR*) *gene*** appear to be causative factors in the development not only of **toxic adenoma of the thyroid** but also of **familial nonautoimmune hyperthyroidism** and **sporadic nonautoimmune hyperthyroidism**. All three of these conditions result in an individual with hyperthyroidism. Most individuals who present with TSHR gene mutations possess enlarged thyroids, but the histology of their thyroid glands differs from those with Graves disease because of the absence of lymphoid infiltration (a characteristic of the thyroid glands of individuals with Graves disease).

C. Control of hormone secretion. The parenchymal cells of endocrine glands not only manufacture and secrete the hormones, but many of them also store them until it is time for their release. It has been demonstrated that the release of certain hormones, such as insulin and growth hormone, is strictly regulated by the concentration of the particular hormone in the bloodstream; thus, a high concentration of a particular hormone causes the gland to stop releasing it, whereas a low concentration of the hormone triggers its release (a system of negative feedback). The release of other hormones may depend on environmental clues, such as the day/night cycle, which affects the secretion of adrenocorticotropic hormone (ACTH) so that its highest serum concentration occurs between 8 and 9 AM. Still other glands possess the capability of autoregulation because of the presence of paracrine and autocrine hormones manufactured and released by special cells of the endocrine gland. Finally, some glands are under the control of the central nervous system, where preganglionic sympathetic nerve fibers (in the case of suprarenal medulla) and, in some cases, postganglionic nerve fibers (in the case of renin, glucagon, and insulin) trigger the release of the hormone.

III. PITUITARY GLAND (HYPOPHYSIS) AND HYPOTHALAMUS

The **pituitary gland** lies below the hypothalamus in a bony housing known as the **hypophyseal fossa**, a depression in the **sella turcica** of the sphenoid bone located in the base of the middle cranial fossa of the skull.

The **hypothalamus** is the region of the diencephalon of the brain that possesses nuclei that are structurally and functionally linked to the pituitary gland. The structural link is via a series of axons whose cell bodies are located in the **supraoptic** and **paraventricular** nuclei of the hypothalamus. These axons form the **hypothalamo-hypophyseal tract** and terminate in the pars nervosa of the pituitary gland where they store and, when needed, release their hormones. The functional connection is via **releasing hormones** that are synthesized in the **arcuate**, **paraventricular** (and **medial paraventricular**), **periventricular**, **ventromedial**, and **dorsal nuclei** of the hypothalamus. These hormones, synthesized by the neuron cell bodies located in these nuclei and released from the axon terminals, enter the **primary capillary bed** in the median eminence. The hormones then make their way, via the **hypophyseal portal system**, to a **secondary capillary bed** in the anterior lobe of the pituitary gland, leave the capillary bed, and bind to their respective target cells in the anterior pituitary.

The relatively small **pituitary gland** weighs only about 0.6 g in males and 1.2 g in pregnant females or females who have given birth to two or more children. The pituitary is divided into two major subdivisions, the **adenohypophysis** and the **neurohypophysis** (Fig. 11.1). Each subdivision is derived from a distinct embryonic analog, which is reflected in its unique cellular constituents and functions.

A. The adenohypophysis, also called the *anterior pituitary gland* (Figs. 11.1 and 11.2), originates from an ectodermal diverticulum of the stomodeum (*Rathke pouch*). It is subdivided into the **pars distalis**, **pars intermedia**, and **pars tuberalis**.

1. The **pars distalis** is supported by a connective tissue capsule and framework. It consists of irregular cords composed of two types of parenchymal cells, **chromophils** and **chromophobes**, lying adjacent to **fenestrated** capillaries.

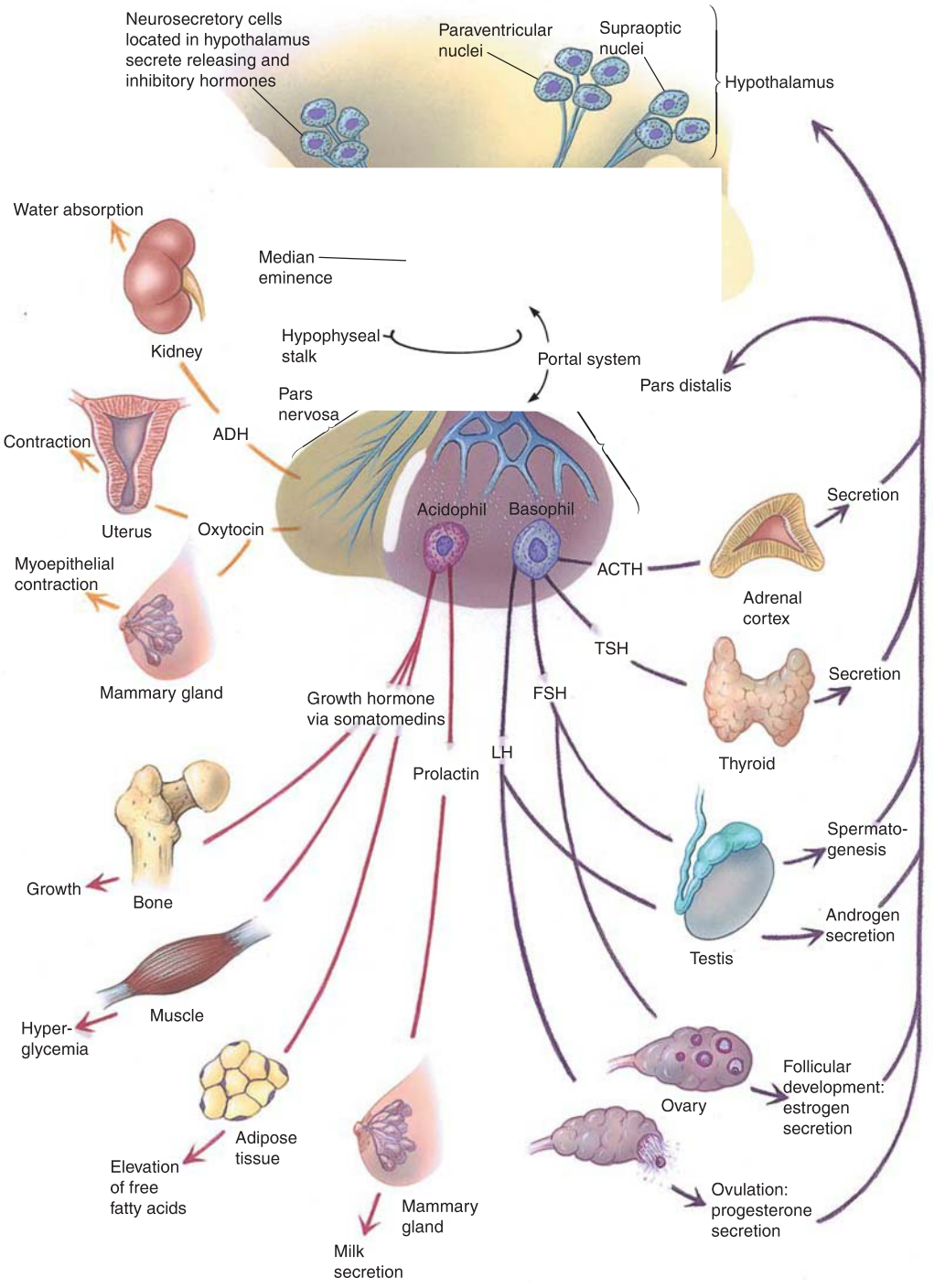


FIGURE 11.1. An illustration of the pituitary gland, showing its connections with the hypothalamus, the hormones it releases, and the effects of these hormones on organs and tissues of the body. ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone. (From Gartner LP. *Color Atlas of Histology*. 7th ed. Baltimore, MD: Wolters Kluwer; 2018:275.)

a. Chromophils (Fig. 11.3)

(1) Overview. Chromophils are parenchymal cells that stain intensely because of their hormone-containing secretory granules. They synthesize, store, and release several hormones. They are regulated by specific **stimulatory** and **inhibitory hormones** produced

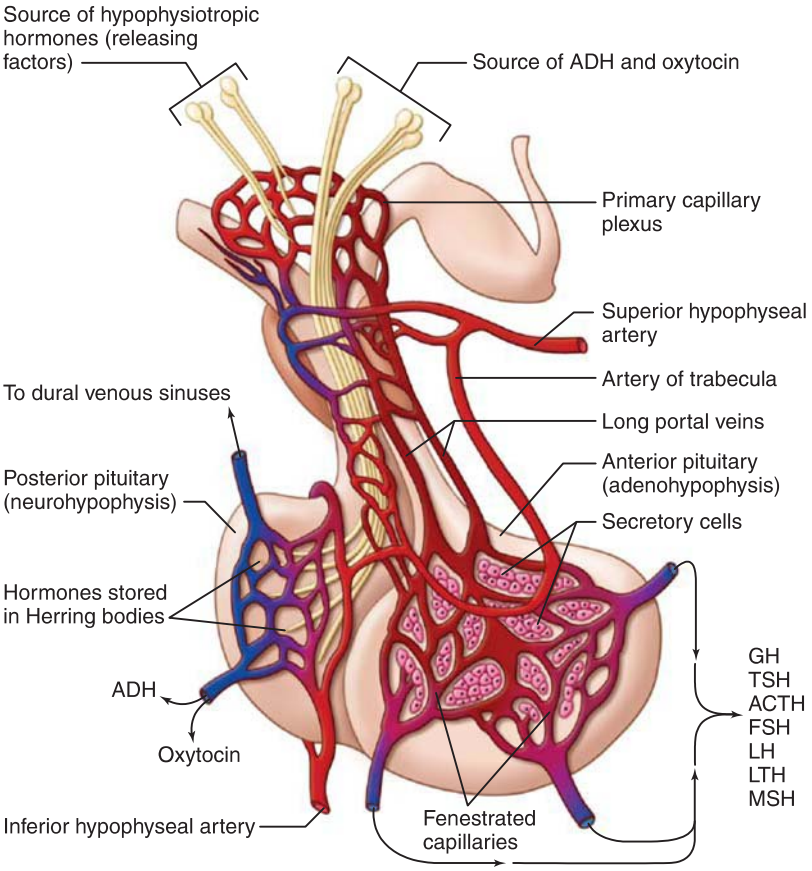


FIGURE 11.2. A diagram of the pituitary gland showing its connections to the hypothalamus, sites of hormone synthesis and storage, and vascularization. The adenohypophysis is shown at the right and consists of the pars distalis, pars tuberalis, and pars intermedia (not labeled). The neurohypophysis consists of the infundibulum (stalk) and pars nervosa. Various releasing and inhibiting hormones stored in the median eminence are transferred, via the hypophyseal portal system, to the pars distalis. ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; LTH, prolactin; MSH, melanocyte-stimulating hormone; TSH, thyroid-stimulating hormone. (Reprinted with permission from Morton P, Fontaine D. *Critical Care Nursing*. 10th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012:959.)

by neurons, referred to as **neurosecretory cells**, in the **hypothalamus**. These hormones are conveyed to the pars distalis via a system of portal blood vessels originating in the **median eminence**.

(2) Chromophils are classified into two types, acidophils and basophils, depending on the dyes they bind using special histologic stains. With hematoxylin–eosin stain, the distinction between the two cell types is much less obvious.

(a) Acidophils (Tables 11.1 and 11.2) bind acidic dyes and often stain **orange** or **red**. They are small cells of two subtypes: somatotrophs and mammotrophs.

1. **Somatotrophs** constitute about 50% of the chromophils and produce **somatotropin** (**growth hormone**). They are stimulated by **somatotropin-releasing hormone** (**SRH**) and are inhibited by **somatostatin**.
2. **Mammotrophs** (**lactotrophs**) constitute about 10% of the chromophil population, except in multiparous women where they may be as high as 30%. Mammotrophs produce **prolactin**, which is stored in small secretory granules. They are stimulated by **prolactin-releasing hormone** and **thyrotropin-releasing hormone** (**TRH**) and are inhibited by **dopamine** (previously designated as **prolactin-inhibiting hormone** [**PIH**]).

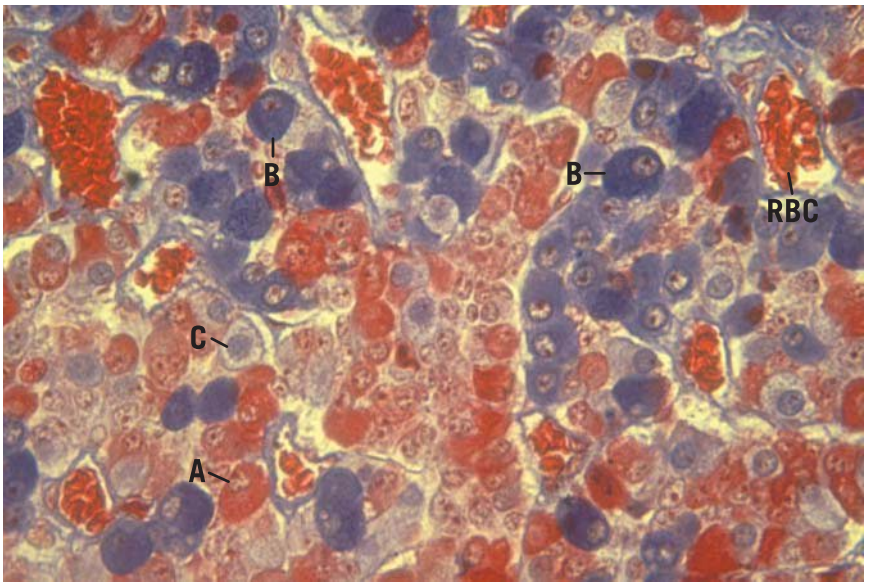


FIGURE 11.3. A light micrograph of cells in the pars distalis of the adenohypophysis. The two types of chromophil cells are easily identified using the trichrome stain. Basophils (B) stain blue, and acidophils (A) stain red. Chromophobes (C) are smaller and show little affinity for the stain. Many erythrocytes (red blood cells [RBCs]) are present in the capillaries (×300).

table 11.1 Physiologic Effects of Pituitary Hormones

Cell	Hormone	Major Function
Hormones released by the pars distalis		
Acidophils		
Somatotrophs	Somatotropin (growth hormone)	Increases metabolism in most cells; indirectly stimulates epiphyseal plate, growth of long bones via production of insulin-like growth factors I, II
Mammotrophs (lactotrophs)	Prolactin	Development of mammary gland during pregnancy, milk synthesis during lactation
Basophils		
Corticotrophs	POMC whose by-products are ACTH, MSH, and lipotropin	ACTH stimulates glucocorticoid secretion by zona fasciculata cells of adrenal cortex MSH stimulates melanocytes to manufacture melanin pigments Lipotropin also stimulates melanocytes to manufacture melanin, but also mobilizes lipids by inducing lipolysis and the formation of steroids
Gonadotrophs	FSH	Stimulates growth of secondary ovarian follicles, estrogen secretion in women; stimulates spermatogenesis via production of androgen-binding protein in Sertoli cells in men
	LH or ICSH	Ovulation, formation of corpus luteum, and progesterone secretion in women; testosterone synthesis by Leydig cells of testis in men
Thyrotrophs	TSH	Stimulates synthesis and release of T_3, T_4 by follicular cells
Hormones released by the pars nervosa		
Neurosecretory cells of hypothalamus (primarily in the paraventricular nucleus)	Oxytocin	Induces contraction of smooth muscle in wall of uterus at parturition and in myoepithelial cells of mammary gland during nursing
Neurosecretory cells of hypothalamus (primarily in the supraoptic nucleus)	ADH	Renders kidney collecting tubules permeable to water, which is resorbed to produce a concentrated urine; constricts smooth muscle in wall of arterioles

ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; FSH, follicle-stimulating hormone; ICSH, interstitial cell–stimulating hormone; LH, luteinizing hormone; MSH, melanocyte-stimulating hormone; POMC, pro-opiomelanocortin; TSH, thyroid-stimulating hormone.

table 11.2 Hormones of the Hypothalamus

Hormone	Nucleus	Primary Functions
Oxytocin	Primarily the paraventricular nucleus	Induces contraction of smooth muscle in wall of uterus at parturition and in myoepithelial cells of mammary gland during nursing
ADH; vasopressin	Primarily the supraoptic nucleus	Renders kidney collecting tubules permeable to water, which is resorbed to produce a concentrated urine; constricts smooth muscle in wall of arterioles
CRH	Arcuate, medial paraventricular, and periventricular nuclei	Induces the release of POMC by the corticotrophs of the anterior pituitary
Dopamine	Arcuate nucleus	Inhibits prolactin release by mammotrophs (lactotrophs) of the anterior pituitary
GnRH	Arcuate, dorsal, paraventricular, and ventromedial nuclei	Induces the release of LH and FSH by gonadotrophs of the anterior pituitary
Somatostatin	Arcuate nucleus	Inhibits somatotropin release by the somatotrophs of the anterior pituitary
SRH (also known as GHRH)	Arcuate nucleus	Induces the release of somatotropin (growth hormone) by the somatotrophs of the anterior pituitary
TRH	Dorsal, paraventricular, and ventromedial nuclei	Induces the release of TSH by the thyrotrophs as well as prolactin by the mammotrophs (autotrophs) of the anterior pituitary

ADH, antidiuretic hormone; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GHRH, growth hormone–releasing hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; POMC, pro-opiomelanocortin; SRH, somatotropin-releasing hormone; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

CLINICAL CONSIDERATIONS

Growth hormone has been promoted unscrupulously as a possible anti-aging factor, and numerous advertisements have claimed "miraculous results of rejuvenation" after its use. Unfortunately, those claims have not been substantiated; instead, various adverse effects have been documented. Some of these include edema, muscle pain, atrial fibrillation, and hyperglycemia, which resolve themselves once the hormone use is discontinued. Currently, the US Food and Drug Administration disapproves of such "off-label" use.

(b) Basophils (Tables 11.1 and 11.2) bind basic dyes and typically stain **blue**. They include three subtypes: corticotrophs, thyrotrophs, and gonadotrophs.

1. **Corticotrophs** constitute about 10% of the chromophil population. Corticotrophs produce **pro-opiomelanocortin (POMC)** whose by-products are **ACTH**, **melanocyte-stimulating hormone** (**MSH**), and **lipotropic hormone** (**LPH**), a precursor of β-endorphin. They are stimulated by **corticotropin-releasing hormone** (**CRH**).
2. **Thyrotrophs** constitute about 5% of the chromophil population, produce **TSH**, and are stimulated by **TRH**.
3. **Gonadotrophs** constitute about 10% of the chromophil population. They produce **FSH** and **luteinizing hormone** (**LH**) in both sexes, although in men, the latter is sometimes referred to as **interstitial cell–stimulating hormone** (**ICSH**). Gonadotrophs are stimulated by **gonadotropin-releasing hormone** (**GnRH**), also known as LH-releasing hormone (LHRH).

b. Chromophobes (Fig. 11.3), poorly staining parenchymal cells, appear as small cells under light microscope; the cells lack (or have only a few) secretory granules and are arranged close to one another in clusters. At times they resemble degranulated chromophils in the electron microscope, suggesting that they may represent different stages in the life. They may also represent undifferentiated cells that are capable of differentiating into various types of chromophils.

c. Folliculostellate cells are found to be numerous in the pars distalis and lie between the chromophils and chromophobes. They produce many peptides that are believed to regulate the production of pars distalis hormones via a paracrine effect. These cells possess long processes that form gap junctions with processes of other folliculostellate cells.

2. The **pars intermedia** lies between the pars distalis and pars nervosa and contains many **colloid-containing cysts** (**Rathke cysts**) that are lined by cuboidal cells. It also possesses **basophilic cells**, which sometimes extend into the pars nervosa. These cells secrete the **prohormone POMC**, which is cleaved to form **ACTH**, **lipotropin**, and **MSH**. In humans, MSH acts to induce melanocytes to produce melanin and may act in various ways to modulate inflammatory responses throughout the body, and it may play a role in controlling stores of body fat.
3. The **pars tuberalis** surrounds the distal part of the infundibulum (hypophyseal stalk) and is composed of cuboidal **basophilic cells**, arranged in cords along an abundant capillary network. These cells may secrete FSH and LH, but this has not been confirmed.

CLINICAL CONSIDERATIONS

Pituitary adenomas, common tumors of the anterior pituitary, are of three types: benign adenomas, invasive adenomas, and carcinomas. Fortunately, about 65% are benign, less than 1% are carcinomas, and about 34% are invasive. Additionally, tumors that are smaller than 10 mm in diameter are referred to as microadenomas, whereas those larger than 10 mm in diameter are known as macroadenomas. As these tumors increase in size, they frequently destroy surrounding bone and neural tissues and are treated by surgical removal. Because the adenomas are derived from hormone-producing parenchymal cells, they will produce an excess of the hormone or hormones that the normal cells produce. An example of such overproduction of hormone is **Cushing disease**, in which an excess amount of **ACTH** is produced, resulting in the release of an overabundance of cortisol (as well as, to some extent, aldosterone and androgens) by the suprarenal glands resulting in fat accumulation above the clavicles, in the back of the neck (buffalo hump), the trunk, and the face (moon face, which is characteristic of this disease). Patients with Cushing syndrome also exhibit an elevated anti-inflammatory effect of cortisol resulting in being infection-prone. Moreover, Cushing disease patients present with edema, hypertension, diabetes, troubles with wound healing, thinning of their hair, irritability, anxiety, depression, and even the possibility of psychosis.

B. The neurohypophysis (Figs. 11.1 and 11.2; Table 11.1) is also called the *posterior pituitary gland*.

It originates from an evagination of the hypothalamus and is divided into the **infundibulum**, which is continuous with the hypothalamus, and the **pars nervosa**, or main body of the neurohypophysis.

1. **Hypothalamo-hypophyseal tract**
   a. This tract contains the unmyelinated axons of **neurosecretory cells** whose cell bodies are located in the **supraoptic** and **paraventricular nuclei** of the hypothalamus.
   b. It transports **oxytocin** and **antidiuretic hormone** (**ADH**; **vasopressin**), each bound to **neurophysin** (a binding protein specific for each hormone), to the pars nervosa (Table 11.2). Oxytocin binds to neurophysin I whereas ADH binds to neurophysin II. Additionally, acetylcholine (ACh) and adenosine triphosphate (ATP) are transported to the pars nervosa by the axons that compose the hypothalamo-hypophyseal tract.
2. The **pars nervosa** contains the distal ends of the hypothalamo-hypophyseal axons and is the site where the neurosecretory granules in these axons are stored in accumulations known as **Herring bodies**. It releases oxytocin and ADH into fenestrated capillaries in response to nerve stimulation.
3. **Pituicytes** are glial-like cells that support axons in this region and occupy approximately 25% of the volume of the pars nervosa. These cells possess numerous cytoplasmic processes and contain lipid droplets, intermediate filaments, and pigments.

CLINICAL CONSIDERATIONS

Diabetes insipidus results from inadequate amounts of ADH; it is discussed in Chapter 16.

C. Vascularization of the pituitary gland

1. **Arterial supply** is from two pairs of **hypophyseal arteries** derived from the internal carotid artery. The right and the left **superior** hypophyseal arteries serve the pars tuberalis, infundibulum, and median eminence. The right and left **inferior** hypophyseal arteries serve mostly the pars nervosa.

2. **Hypophyseal portal system** (Figs. 11.1 and 11.2)
   a. The **primary capillary plexus**, located in the **median eminence**, where stored hypothalamic neurosecretory hormones enter the blood, consists of fenestrated capillaries branching off the superior hypophyseal arteries. It is drained by **hypophyseal portal veins**, which descend through the infundibulum into the adenohypophysis.
   b. The **secondary capillary plexus** consists of **fenestrated** capillaries derived from the hypophyseal portal veins. This plexus is located in the **pars distalis**, where neurosecretory hormones leave the blood to stimulate or inhibit the parenchymal cells.

CLINICAL CONSIDERATIONS

Sheehan syndrome is necrosis of the anterior pituitary gland because of a sudden reduction in blood pressure of the newborn as a result of postpartum hemorrhage. The bulk of the anterior pituitary becomes necrotic and only the peripheral parenchymal cells remain healthy and viable. The functionality of the adenohypophysis depends on the severity of the necrotic event; the wider the parenchymal destruction, the less function remains. Interestingly, the neurohypophysis is usually unaffected because it has a different blood supply.

Patients afflicted with **hemochromatosis** (**iron overload**), whether as a function of heredity or acquired because of multiple transfusions, present with iron deposits in the pituitary gland, especially in the gonadotrophs. This condition is known as **hemosiderosis** and is fortunately treatable either by phlebotomy or by chelating the iron with one of the available chelating agents on the pharmaceutical armamentarium.

D. Regulation of the pars distalis (Figs. 11.1 and 11.2)

1. Neurosecretory cells in the hypothalamus synthesize specific hormones that enter the hypophyseal portal system and stimulate or inhibit the parenchymal cells of the pars distalis (Table 11.2).
2. The hypothalamic neurosecretory cells in turn are regulated by the level of hormones in the blood (**negative feedback**) or by other physiologic (or psychological) factors.
3. Some hormones (e.g., thyroid hormones, cortisol) exert negative feedback on the pars distalis directly.

IV. THYROID GLAND (Fig. 11.4)

The thyroid gland, composed of two lobes connected by an **isthmus**, is surrounded by a dense irregular collagenous connective tissue capsule, in which (posteriorly) the **parathyroid glands** are embedded. Septa from the capsule subdivide the thyroid gland into lobules containing **follicles**. These septa also serve as conduits for blood vessels, lymphatic vessels, and nerves.

A. Thyroid follicles are spherical structures filled with *colloid*, a viscous gel consisting mostly of *iodinated thyroglobulin* (Fig. 11.5).

1. Surrounding the colloid within each follicle is a single layer of epithelial cells, called **follicular cells**, which synthesize thyroid hormones. In addition, one or more **parafollicular cells** occasionally lie sandwiched between the follicular cells and their basal lamina, which separates these cells from the abundant network of **fenestrated capillaries** in the connective tissue.

B. Follicular cells (Fig. 11.6) are normally cuboidal, but they become columnar when stimulated and squamous when inactive.

They possess a distended rough endoplasmic reticulum (RER) with many ribosome-free regions, a supranuclear Golgi complex, many lysosomes, rod-shaped mitochondria, and many small **apical vesicles**, which are involved in the transport and release of thyroglobulin and enzymes into the colloid. These cells also display short, blunt microvilli that extend into the colloid. Synthesis and release of the thyroid hormones **thyroxine** (T_4) **and triiodothyronine** (T_3) are triggered by **TSH**, which binds to G protein–linked receptors on the basal surface of follicular cells, as depicted by the sequence of events illustrated in Figure 11.7.

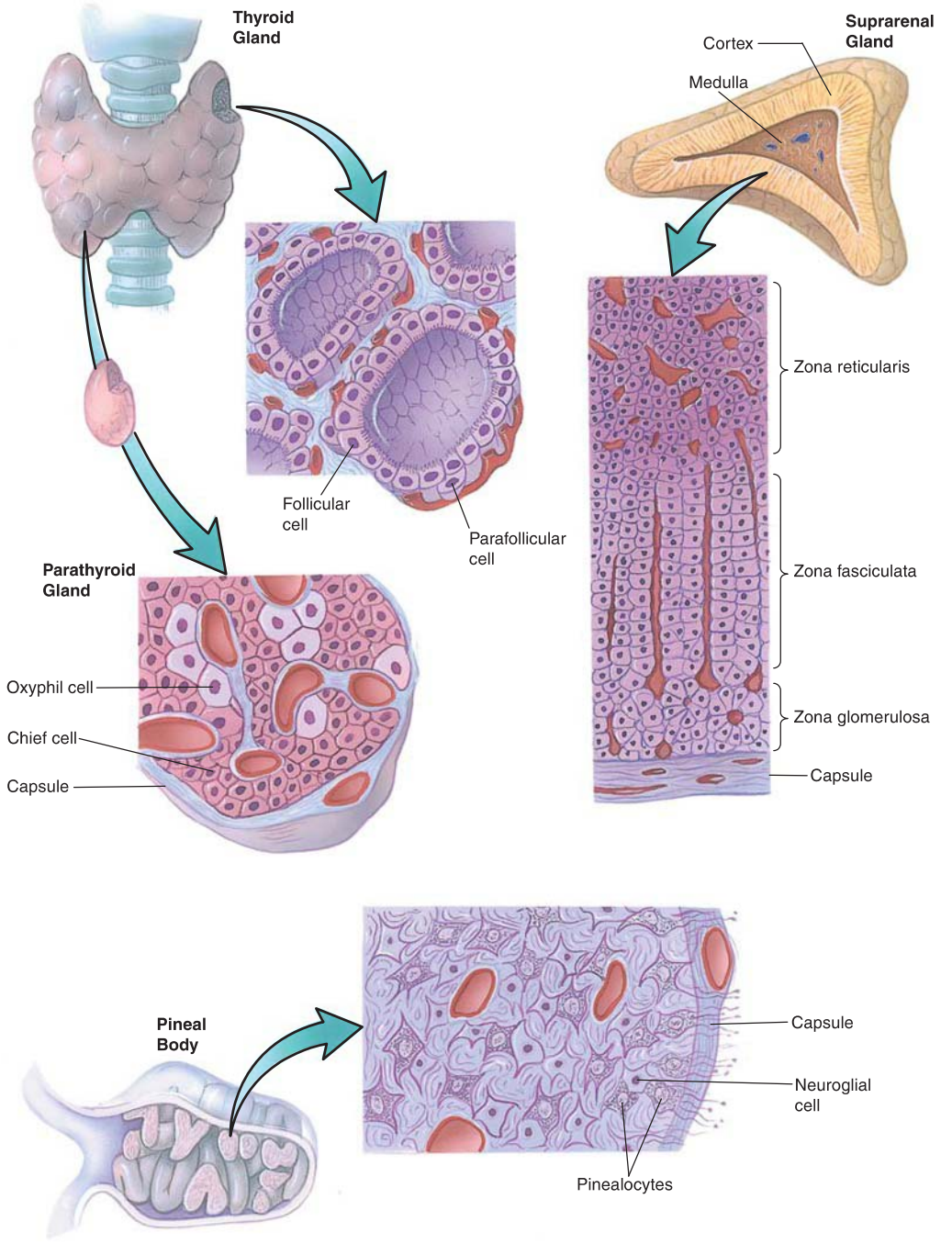


FIGURE 11.4. A diagram showing features of the thyroid, parathyroid, adrenal, and pineal glands. (From Gartner LP. *Color Atlas of Histology*. 7th ed. Baltimore, MD: Wolters Kluwer; 2018:276.)

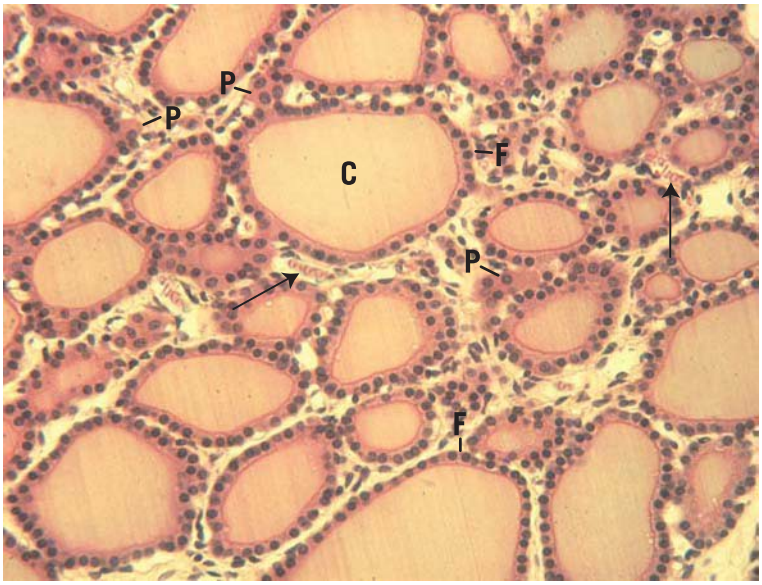


FIGURE 11.5. A light micrograph showing follicles within the thyroid gland. Each follicle is surrounded by a layer of follicular cells (F) and contains a central colloid-filled region (C). The follicular cells synthesize and secrete thyroid hormones bound within a large protein molecule, thyroglobulin, which makes up most of the colloid. A second type of endocrine cell, the parafollicular cell (P), is also present in the thyroid gland. It has no contact with the colloid and is often found in small clusters at or near the basal surfaces of the follicular cells. The parafollicular cell synthesizes calcitonin and releases it into the rich network of capillaries (*arrows*) existing between the follicles (×150).

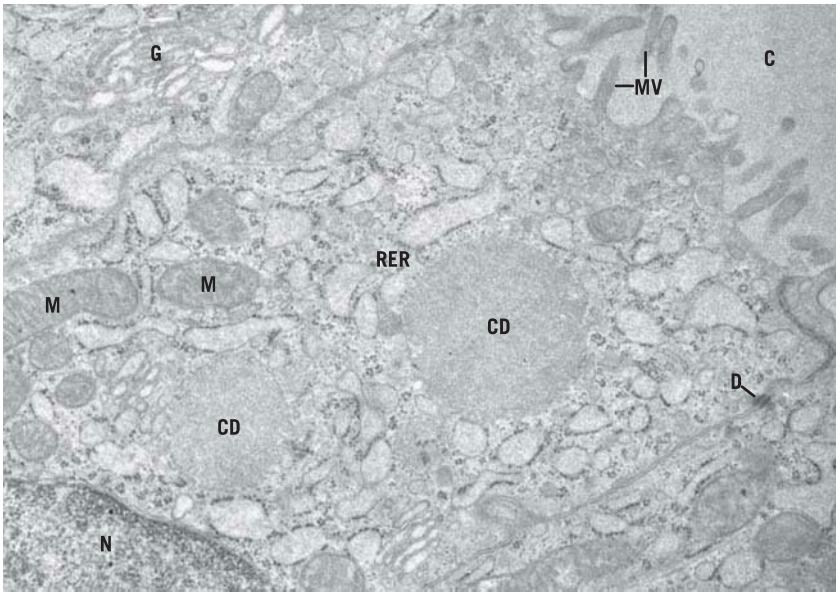


FIGURE 11.6. Electron micrograph of thyroid follicular cells. Two large colloid droplets (CD), a distended rough endoplasmic reticulum (RER) with many ribosome-free regions, and a Golgi apparatus (G) are observed. Microvilli (MV) extend into the lumen of a follicle-containing colloid (C). Also present are mitochondria (M), a nucleus (N), and a desmosome (D) (×7,500).

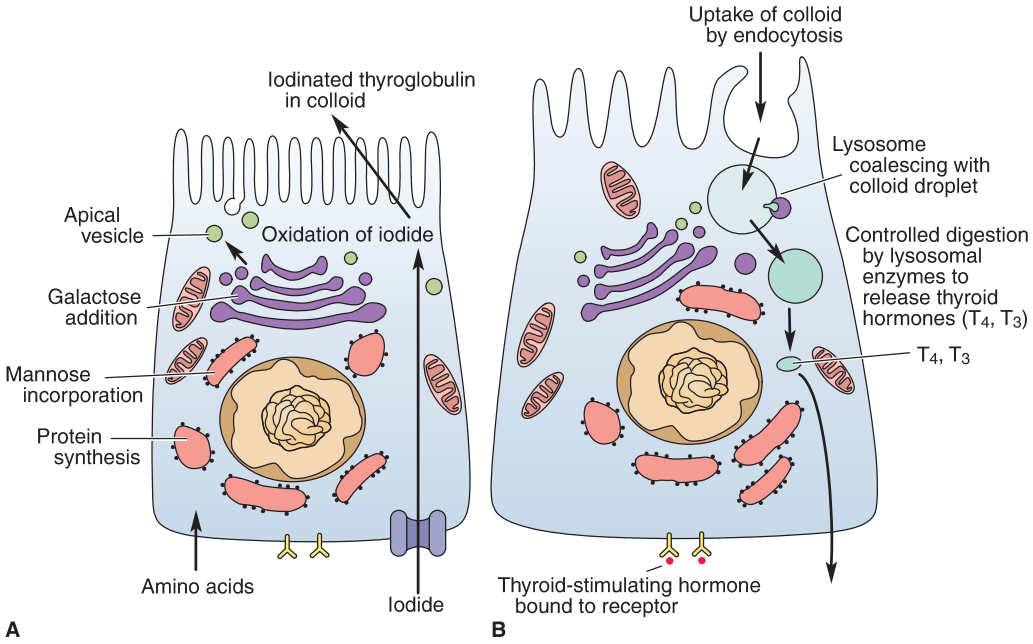


FIGURE 11.7. Synthesis and release of thyroxine (T_4) and triiodotyrosine (T_3) by follicular cells of the thyroid gland. **A.** Thyroglobulin is synthesized like other secretory proteins. Circulating iodide (I^-) is actively transported into the cytosol via sodium iodide symporters, so that the iodide concentration in the follicular cells becomes 20 to 30 times greater than it is in the blood. Iodide leaves the follicular cell to enter the colloid via pendrin, an iodide–chloride transporter. At the same time, noniodinated thyroglobulin, packaged with the enzyme thyroid peroxidase, is also being released into the colloid. At the colloid follicular cell interface, thyroid peroxidase oxidizes the iodide to form iodine (I) and iodinates tyrosine residues on the thyroglobulin molecule, forming monoiodotyrosine and diiodotyrosine residues; therefore, iodination occurs mostly at the apical plasma membrane. A rearrangement, by oxidative coupling, of the neighboring iodinated tyrosine residues of thyroglobulin in the colloid produces T_3 and T_4. **B.** Binding of thyroid-stimulating hormone to receptors on the basal surface stimulates follicular cells to become columnar and to form apical pseudopods, which engulf colloid by endocytosis. After the colloid droplets fuse with lysosomes, controlled hydrolysis of iodinated thyroglobulin liberates T_3 and T_4 into the cytosol. These hormones move basally and are released basally to enter the bloodstream and lymphatic vessels, where they bind with the carrier protein, thyroxine-binding globulin, that ferries the hormones to their target cells. (Adapted with permission from Junqueira LC, Carneiro J, Kelley RO. *Basic Histology.* 9th ed. Stamford, CT: Appleton & Lange; 1998:403; Fawcett DW. *Bloom and Fawcett: A Textbook of Histology.* 12th ed. New York, NY: Chapman & Hall; 1994:496.)

CLINICAL CONSIDERATIONS

Graves disease, characterized by a diffuse **enlargement of the thyroid gland** and **protrusion of the eyeballs** (exophthalmic goiter), is associated with the presence of columnar-shaped thyroid follicular cells, excessive production of thyroid hormones, and decreased amounts of follicular colloid. The disease is caused by the binding of autoimmune immunoglobulin G (IgG) antibodies to TSH receptors, which stimulates the thyroid follicular cells. Additionally, inflammatory cells, such as T cells, neutrophils, and macrophages, invade the connective tissues of the retro-orbital region and release cytokines that activate fibroblasts not only to increase their production of proteoglycans but also to differentiate into fat cells. Because proteoglycans readily attract Na^+ ions, which attract water molecules, the connective tissue volume increases; moreover, the additional number of fat cells also acts to increase the volume of the retro-orbital connective tissue, putting an increased pressure on the back of the eyeball, pushing it forward, resulting in protrusion of the eye.

C. **Parafollicular cells, also called *clear* (*C*) *cells* because they stain less intensely than thyroid follicular cells (Figs. 11.5 and 11.8), are present singly or in small clusters of cells between the follicular cells and basal lamina.** They belong to the population of **DNES cells** and possess elongated mitochondria, substantial amounts of RER, a well-developed Golgi complex, and many membrane-bound dense secretory granules that house calcitonin, a polypeptide hormone that they synthesize and release in response to high blood calcium levels.

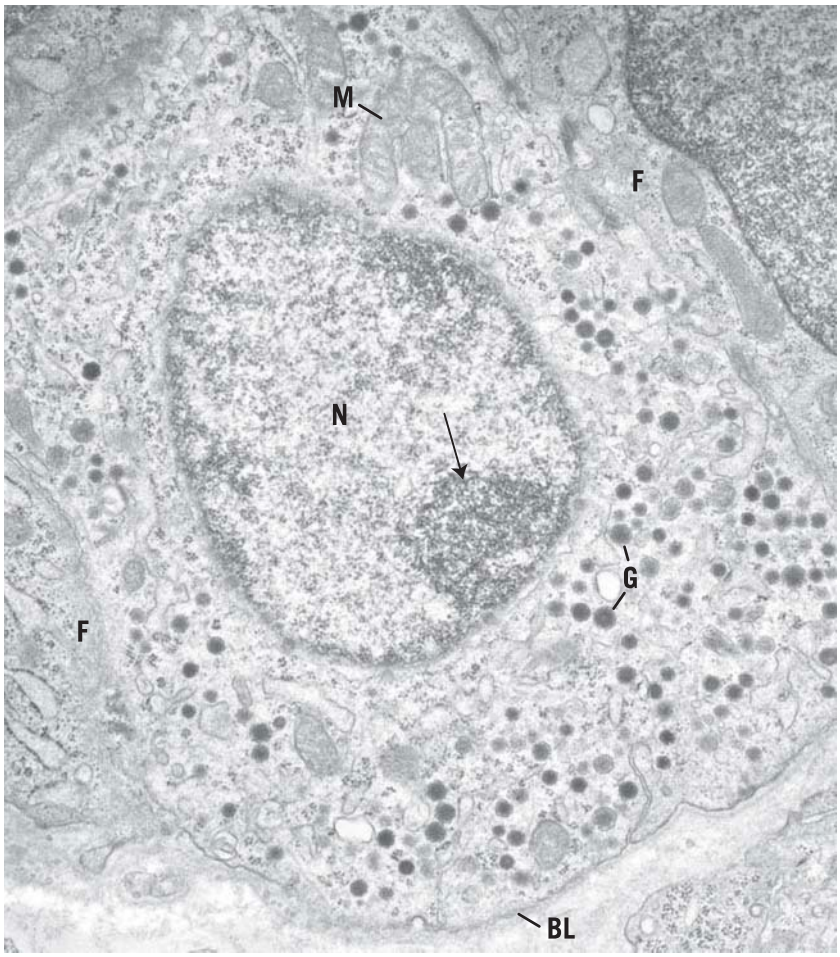


FIGURE 11.8. Electron micrograph of a parafollicular cell (clear cell, C cell) in the thyroid gland. This cell lies between the follicular cells (F) within the basal lamina (BL) enveloping the follicle. Its nucleus (N) displays a nucleolus (*arrow*), and its cytoplasm possesses elongated mitochondria (M). In response to high levels of calcium in the blood, the parafollicular cell releases the hormone calcitonin by exocytosis of the dense granules (G) in its cytoplasm. The calcitonin enters nearby fenestrated capillaries and lowers blood calcium levels by inhibiting osteoclast bone resorption throughout the body (×7,000).

D. Physiologic effects of thyroid hormones

1. T_4 and T_3 act on a variety of target cells. These hormones **increase the basal metabolic rate** and thus promote heat production. They have broad effects on gene expression and the induction of protein synthesis. T_4 has a much longer half-life (approximately 6 days vs. less than a day) but is much less active than T_3. Both hormones have to enter the nucleus to perform their function.
2. **Calcitonin** functions primarily to lower blood calcium levels by inhibiting bone resorption by osteoclasts.

CLINICAL CONSIDERATIONS

Goiter, the enlargement of the thyroid gland, is caused by a number of reasons, but the major origin in undeveloped countries is the insufficient dietary intake of iodine (**simple goiter**), which is less than 10 μg/d. Additional reasons for the occurrence of goiter are due to problems with the synthesis of thyroid hormone because of congenital enzyme deficiencies, diet that includes substances that are considered goitrogens (cruciferous vegetables such as bok choy, cabbage, broccoli, etc.), certain drugs (such as thiocyanates, phenytoin, carbamazepine, etc.), autoimmune diseases that destroy follicular cells of the thyroid, neoplasms affecting the thyroid gland, and pituitary tumors that involve basophils that produce TSHs.

V. PARATHYROID GLANDS (Fig. 11.4)

A. Overview

1. The parathyroid glands are four small glands that lie on the posterior surface of the thyroid gland, embedded in its connective tissue capsule, whose septa penetrate each gland and also convey blood vessels (Fig. 11.4) into its interior. The parathyroid gland parenchyma is composed of two types of cells, **chief cells** and **oxyphil cells**. It should be stressed that the parathyroid gland is ***not*** controlled by the pituitary gland.
2. As the individual ages, the parathyroid glands become infiltrated with fat cells and the number of oxyphil cells increases.

B. Chief cells, small basophilic cells arranged in clusters (Fig. 11.9) of anastomosing cords, surrounded by a rich, fenestrated capillary network, possess a central nucleus, a well-developed Golgi complex, abundant RER, small mitochondria, glycogen, and secretory granules of variable size.

1. **Chief cells** synthesize and secrete **parathyroid hormone** (**PTH**, or **parathormone**), which raises blood calcium levels. High blood calcium levels **inhibit** the production of PTH. The hormone acts on osteoclasts and also induces the decrease in calcium excretion by the thick ascending limb of Henle's loop of the kidney.
2. The cell membrane of chief cells possesses a transmembrane **Ca^{2+} receptor** (**CaSR**) that binds calcium ions. In the presence of Ca^{2+} ions CaSR activates G proteins that shut off the release of parathormone, whereas if Ca^{2+} ions do not bind to CaSR, the inhibitory activity of the G protein is suppressed and the chief cells release parathormone.

C. Oxyphil cells, large, eosinophilic cells that are present singly or in small clusters within the parenchyma of the gland (Fig. 11.9), possess many large, elongated mitochondria, a poorly developed Golgi complex, and only a limited amount of RER. The function of these cells is not known.

D. PTH functions primarily to *increase* blood calcium levels by indirectly stimulating osteoclasts to resorb bone. In concert with calcitonin, the hormone produced and released by the C cells of the

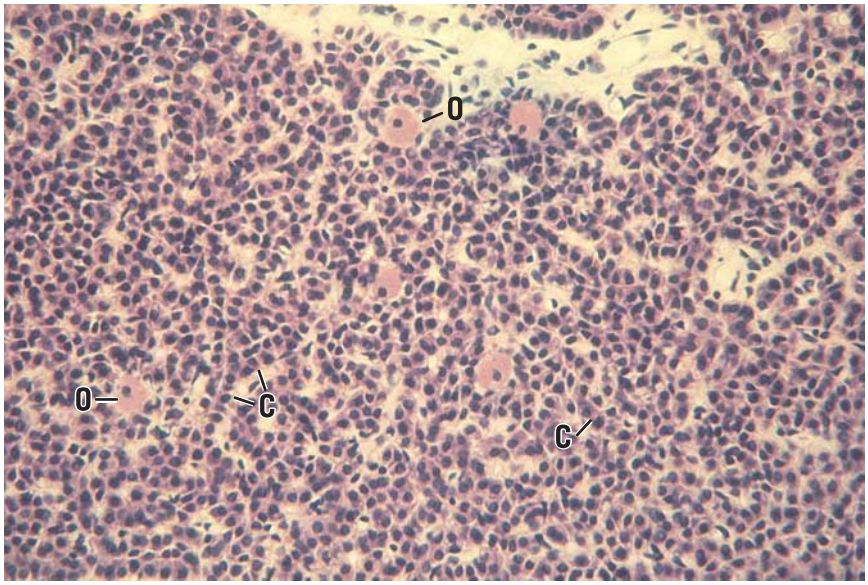


FIGURE 11.9. A light micrograph of the parathyroid gland. Chief cells (C) are small basophilic cells arranged in cords along capillaries. They synthesize and secrete parathyroid hormone that raises blood calcium levels primarily by mobilizing calcium from the bone. Oxyphil cells (O) are also present in the parathyroid gland. They are acidophilic, much larger than the chief cells, and few in number, but they increase in number with age. Oxyphils contain many large elongated mitochondria, but the function of these cells is not known (×150).

thyroid gland, PTH provides a dual mechanism for regulating blood calcium levels. A near absence of PTH (hypoparathyroidism) may be caused by accidental surgical removal of the parathyroid glands, which leads to **tetany**, characterized by hyperexcitability and spastic skeletal muscle contractions throughout the body.

CLINICAL CONSIDERATIONS

Hyperparathyroidism (increased activity of the parathyroid glands with a resultant excess secretion of PTH and consequent bone resorption) may be caused by a benign tumor of the parathyroid glands and is associated with *high* blood calcium levels, which may lead to deposition of calcium salts in the kidneys and the walls of blood vessels. The two types of parathyroidisms are primary and secondary.

Primary parathyroidism is caused mostly by parathyroid adenoma, but other causative factors are tumors of cells outside the parathyroid glands that synthesize and release PTH-like hormone. Clinical symptoms include generalized ectopic calcifications in soft tissues and kidney stones, among others.

Secondary parathyroidism is usually caused by abnormal kidney function resulting in hypocalcemia. Clinical symptoms include ectopic calcification and osteoclastic bone disease.

VI. ADRENAL (SUPRARENAL) GLANDS (Fig. 11.4)

Adrenal glands (although more accurately called *suprarenal glands* in the human, they will be addressed as adrenal glands in this book) lie embedded in fat at the superior pole of each kidney. They are derived from two embryonic sources: the ectodermal neural crest, which gives rise to the **adrenal medulla**, and the mesoderm, which gives rise to the **adrenal cortex**. The adrenal glands are invested by their own collagenous capsule.

A. **The adrenal cortex (Table 11.3) contains parenchymal cells that synthesize and secrete but *do not store* various steroid hormones.** The production of steroid hormones is dependent on a specific protein, **steroidogenic acute regulatory protein**, that facilitates the transport of cholesterol across the outer membranes of mitochondria. The adrenal cortex is divided into three concentric histologically recognizable regions: the **zona glomerulosa**, **zona fasciculata**, **and zona reticularis** (Fig. 11.10).

1. **Zona glomerulosa**, composed of small cells arranged in arch-like cords and clusters, have a few small lipid droplets, an extensive network of smooth endoplasmic reticulum (SER), and mitochondria

table 11.3 Adrenal Gland Cells and Hormones

Cell	Hormone	Function
Adrenal cortex		
Zona glomerulosa	Mineralocorticoids (mostly aldosterone)	Regulates electrolyte, water balance via effect on cells of renal tubules
Zona fasciculata	Glucocorticoids (cortisol, corticosterone)	Regulates carbohydrate metabolism by promoting gluconeogenesis; promotes breakdown of proteins, fat; anti-inflammatory properties; suppresses immune response
Zona reticularis	Weak androgens (dehydroepiandrosterone, androstenedione)	Promotes masculine characteristics
Adrenal medulla		
Chromaffin cells	Epinephrine	Fight-or-flight -or freeze-response; increases heart rate and force of contraction; relaxes bronchiolar smooth muscle; promotes glycogenolysis and lipolysis
	Norepinephrine	Increases cardiac output, rarely used clinically

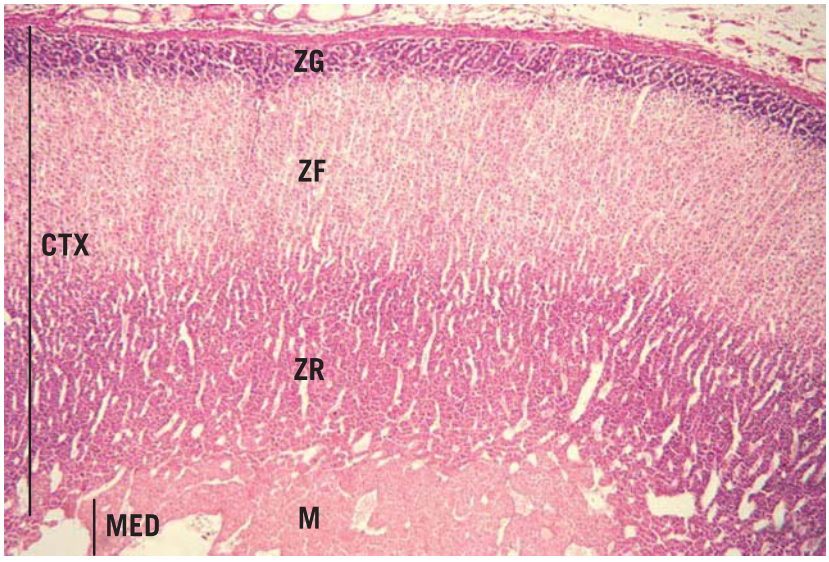


FIGURE 11.10. A light micrograph of the adrenal gland showing the different regions of the cortex (CTX) and a portion of the medulla (MED). Cells in the outermost zona glomerulosa (ZG) are arranged in clusters and secrete mineralocorticoids; cells in the middle zona fasciculata (ZF) are arranged in cords between sinusoidal capillaries and secrete glucocorticoids and a small amount of androgens; and cells of the innermost zona reticularis (ZR) are arranged in anastomosing cords and secrete androgens and small amounts of glucocorticoids. Cells in the adrenal medulla (M), called chromaffin cells, synthesize, store, and secrete epinephrine and norepinephrine (×16).

with **shelf-like cristae**, which synthesize and secrete **mineralocorticoids**, mostly **aldosterone** and some **deoxycorticosterone**. Hormone production is stimulated by **angiotensin II** and **ACTH**.

2. **Zona fasciculata** is composed of columns of cells and **sinusoidal capillaries** oriented perpendicularly to the capsule. These cells contain many lipid droplets and (in tissue sections) appear so vacuolated that they are called **spongiocytes** (Fig. 11.11). Spongiocytes possess spherical mitochondria with **tubular** and **vesicular cristae**, SER, RER, lysosomes, and **lipofuscin pigment granules**. Parenchymal cells of the zona fasciculata synthesize and secrete **glucocorticoids**, namely **cortisol and corticosterone**. Hormone production is stimulated by ACTH (Fig. 11.12).
3. **Zona reticularis** is composed of cells arranged in anastomosing cords. Many large **lipofuscin pigment granules** are common in these cells (Figs. 11.10 and 11.11) and are believed to represent lipid-containing residues of lysosomal digestion. Parenchymal cells of the zona reticularis synthesize and secrete **weak androgens** (mostly **dehydroepiandrosterone** and some **androstenedione**) and perhaps small amounts of glucocorticoids. Hormone production is stimulated by ACTH.

CLINICAL CONSIDERATIONS

Adrenal hypofunction (**adrenal hypocorticism**) is characterized by a deficiency in the secretion of glucocorticoids (mainly **cortisol**) accompanied, frequently, by a reduced **mineralocorticoid** secretion. The three types of adrenal hypofunction are primary, secondary, and tertiary.

Primary (**adrenal**) **hypofunction** (**Addison disease**), a result of greater than 90% destruction of the adrenocortical parenchyma, is most often caused by an autoimmune disease that originates in the adrenal gland. Other causes of Addison disease include neoplasm of the glands, vascular problems resulting in hemorrhage of both adrenal glands, and the aftermath of tuberculosis. The symptoms of Addison disease are low blood pressure; elevated serum potassium levels; diminished serum levels of glucose, bicarbonate, sodium, and chloride; and increased skin pigmentation. Additional symptoms are fatigue and weakness, weight loss, vomiting, weak pulse, and a strong desire for salty foods.

Secondary (**adrenal**) **hypofunction** differs from the primary hypofunction in that the problem originates in the pituitary gland. Usually, it is caused by adenoma of the pituitary with a subsequent lack of **ACTH** production.

Tertiary adrenal hypofunction differs from the secondary hypofunction in that the problem is in the hypothalamus (possibly a tumor), which is not producing **corticotrophin-releasing hormone.**

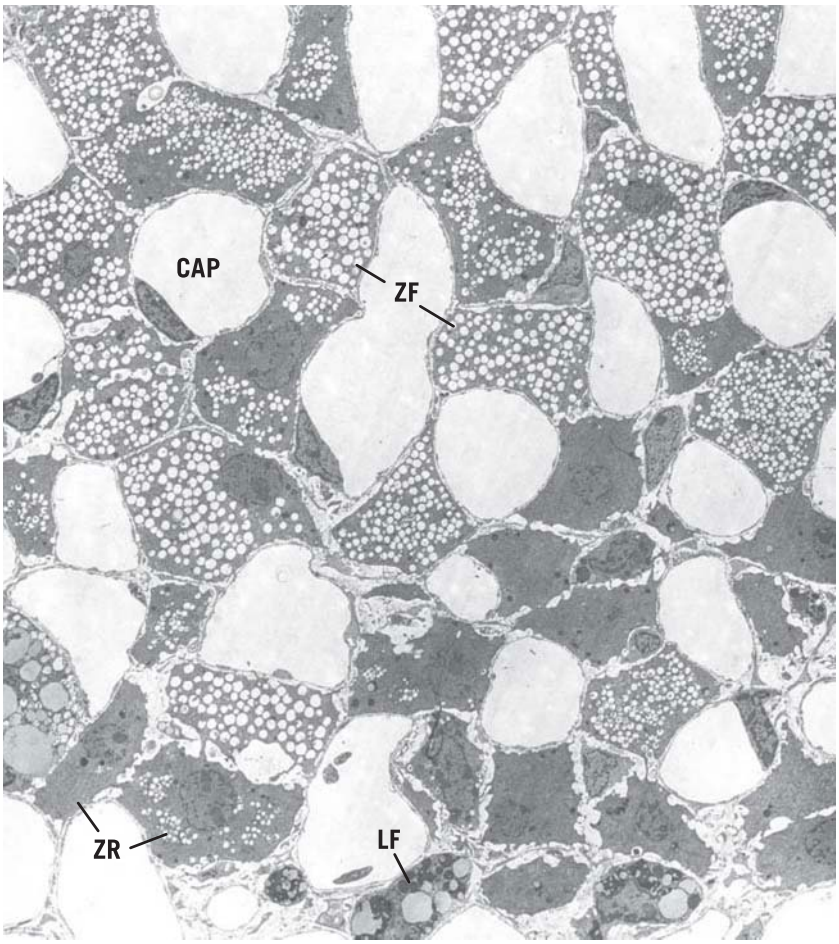


FIGURE 11.11. Cells of the zona fasciculata (ZF) and zona reticularis (ZR) are shown in this very low-power electron micrograph. ZF cells are called spongiocytes because of their appearance, which is caused by the extraction of the many lipid droplets in their cytoplasm that have been removed through the process of fixation and dehydration. The spongiocytes lie next to a rich network of sinusoidal capillaries (CAP), which have been cleared of erythrocytes by perfusion. ZR cells are also observed, and a few of them are filled with large lipofuscin (LF) pigment granules (×1,500).

B. The adrenal medulla (Table 11.3) is completely invested by the adrenal cortex. It contains two populations of parenchymal cells, called **chromaffin cells**, which synthesize, store, and secrete the catecholamines **epinephrine** (approximately 80% of chromaffin cells) and **norepinephrine** (approximately 20% of chromaffin cells). It also contains scattered **sympathetic ganglion cells**.

1. **Chromaffin cells**, large polyhedral cells containing a well-developed Golgi complex, isolated regions of RER, and numerous mitochondria, are arranged in short, irregular cords surrounded by an extensive capillary network. These cells also contain large numbers of membrane-bound granules containing one of the catecholamines, ATP, enkephalins, and **chromogranins**, which may function as binding proteins for epinephrine and norepinephrine.
   a. They are innervated by ACh-containing **preganglionic sympathetic** (**cholinergic**) **fibers**, making these cells analogous in function to postganglionic sympathetic neurons.
   b. ACh released from the nerve fibers causes the opening of calcium channels of the chromaffin cells. The influx of calcium ions results in the exocytosis of epinephrine or norepinephrine.
2. Mostly **epinephrine** is released in case of physiologic stimulus, such as pain, whereas mostly **norepinephrine** is released as a consequence of emotional stimuli. If the stimulus is severe fear or stress, epinephrine release is magnified to get the individual ready for a "fight, flight, or freeze" response.

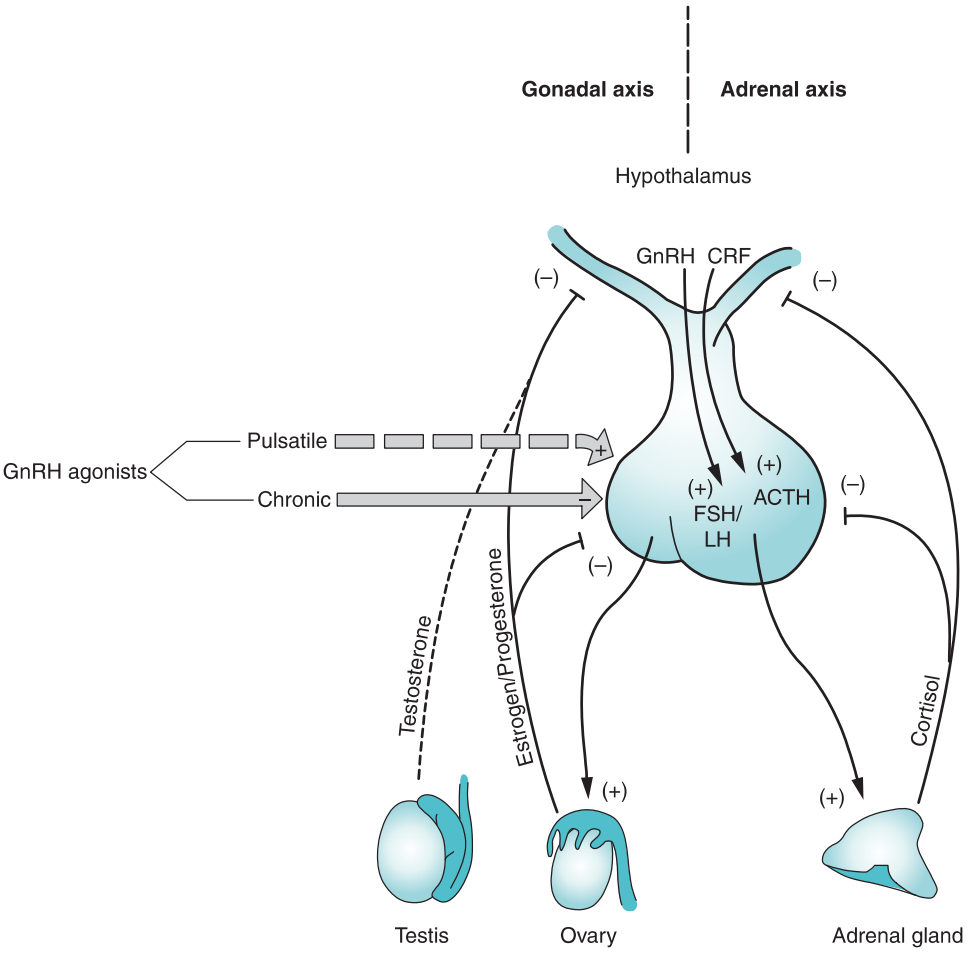


FIGURE 11.12. Regulation of glucocorticoid secretion by the adrenal cortex via stimulation by corticotropin-releasing hormone and adrenocorticotropic hormone (ACTH) and the negative feedback of cortisol at both the pituitary and the hypothalamic levels. CRF, corticotropin-releasing factor; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone. (Reprinted with permission from Rosenfeld G, Loose D. *BRS Pharmacology*. 5th ed. Baltimore, MD: Wolters Kluwer Health; 2009:218.)

CLINICAL CONSIDERATIONS

A **pheochromocytoma** is a tumor arising in catecholamine-secreting chromaffin cells of the adrenal medulla. The tumor is rare, it is found in both sexes, and 90% of the time it is benign. However, its secretion of excessive amounts of epinephrine and norepinephrine leads to **hypertension** (episodic or sustained), although the patient may remain asymptomatic. Increased levels of catecholamines and their metabolites in the urine are diagnostic of pheochromocytoma. If the tumor is detected early and is surgically removed, the hypertension is correctable, but if not, prolonged and sustained hypertension may prove fatal.

C. Blood supply to the adrenal glands **is derived from the superior, middle, and inferior adrenal arteries, which form three groups of vessels: to the capsule, to parenchymal cells of the cortex, and directly to the medulla.**

1. **Cortical blood supply**
   a. A **fenestrated** capillary network bathes cells of the zona glomerulosa.
   b. **Straight**, **discontinuous**, **fenestrated** capillaries supply the zona fasciculata and zona reticularis.

CLINICAL CONSIDERATIONS

Waterhouse–Friderichsen syndrome (hemorrhagic adrenalitis) is a very serious condition where uncontrolled bleeding into the adrenal cortices of both adrenal glands causes them to become necrotic. The underlying cause of the condition is due to a very severe bacterial (or occasionally, viral) infection with any of the following organisms that can cause **bacterial meningitis**: *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Pseudomonas aeruginosa*. Recent studies of the effects of Ebola virus indicate that infections with this virus can also be responsible for this condition. If the condition remains untreated it may have lethal consequences.

2. **Medullary blood supply**
   a. **Venous blood** rich in hormones reaches the medulla via the discontinuous fenestrated capillaries that pass through the cortex.
   b. **Arterial blood** from direct branches of capsular arteries forms an extensive fenestrated capillary network among the chromaffin cells of the medulla.
   c. **Medullary veins** join to form the suprarenal vein, which exits the gland.

VII. PINEAL GLAND (PINEAL BODY, EPIPHYSIS)

A. Overview (Fig. 11.4)

1. The pineal gland projects from the **roof of the diencephalon**. Its capsule is formed of the **pia mater**, from which septa (containing blood vessels and unmyelinated nerve fibers) extend to subdivide it into incomplete lobules. It is composed primarily of **pinealocytes**, comprising approximately 95% of the cells, and **neuroglial cells** (**interstitial cells**), which constitute about 5% of the cells.
2. Secretions of the pineal gland vary with the light and dark cycles of the day, thereby regulating the individual's circadian rhythm. Although the pineal gland is buried deep within the head it receives information about the light and dark conditions from special ganglion cells in the retina of the eye. These ganglion cells send their information about the presence of daylight via the retinohypothalamic tract that projects to the suprachiasmatic nucleus of the hypothalamus from where information reaches the superior cervical sympathetic ganglion whose postganglionic sympathetic fibers reach the pineal gland by riding on the tunica adventitia of blood vessels that supply the pineal.
3. The pineal gland also contains calcified concretions (**brain sand**) in its interstitium (Fig. 11.13). The function of these concretions is unknown, but they increase during short light cycles and decrease during periods of darkness.

B. Pinealocytes **are pale-staining cells with numerous long processes that end in dilations near capillaries.**

1. Pinealocytes contain many secretory granules, microtubules, microfilaments, and unusual structures called **synaptic ribbons**.
2. These cells synthesize and immediately secrete **melatonin** but almost only at night. During the day melatonin synthesis is mostly inhibited by the enzyme **arylalkylamine *N*-acetyltransferase**.

C. Neuroglial (interstitial) cells **resemble astrocytes, with elongated processes and a small, dense nucleus.** They contain microtubules and many microfilaments and intermediate filaments.

CLINICAL CONSIDERATIONS

Melatonin is used to treat jet lag and seasonal affective disorder, an emotional response to shorter daylight hours during the winter.

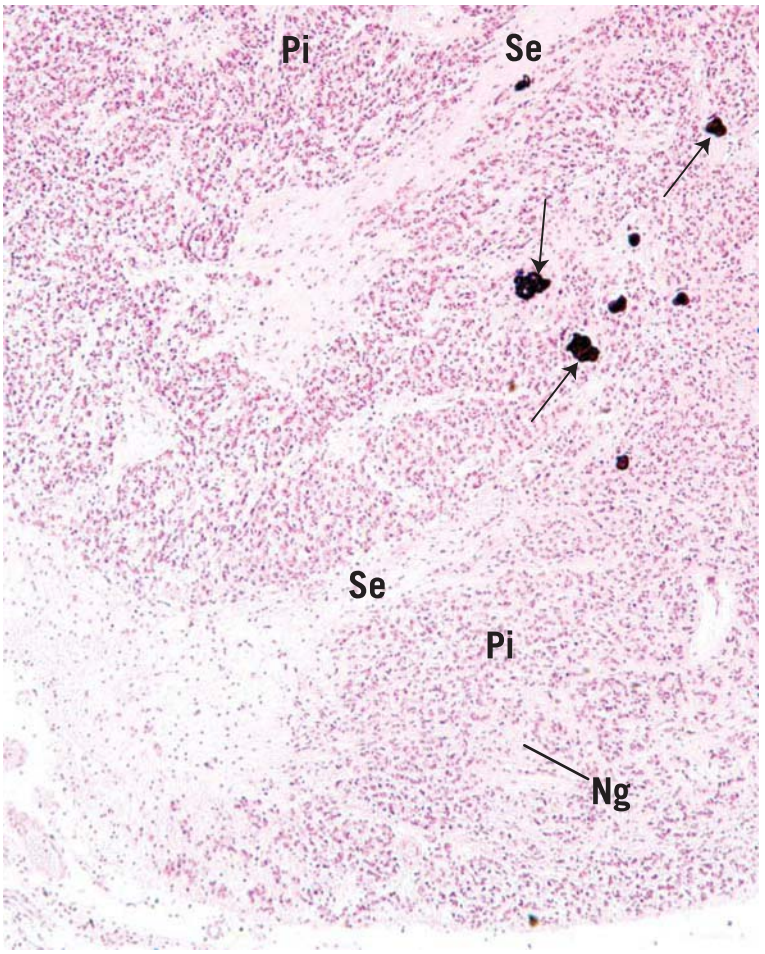


FIGURE 11.13. This low-magnification image of the human pineal gland displays the septae (Se), derived from the capsule formed from the pia mater that subdivides the pineal into incomplete lobules. Note the nuclei of pinealocytes (Pi) that are close to each other as well as the nuclei of neuroglial cells (Ng) that are relatively far from each other. The *arrows* indicate the calcified concretions, known as corpora arenacea or brain sand (*arrows*) (×56).

Review Test

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or completions of the statement. Select the ONE lettered answer that is BEST in each case.

Questions 1 and 2 are related to the following clinical scenario:

A 40-year-old female patient who presented with an enlarged thyroid gland was diagnosed with Graves disease.

1. Which of the following characteristics would be associated with her condition?

(A) Inadequate levels of iodine in her diet
(B) Weight gain
(C) Flattened thyroid follicular cells
(D) Excessive production of thyroid hormones
(E) Increased amounts of follicular colloid

2. A biopsy of the thyroid gland permits the pathologist to rule out sporadic nonautoimmune hyperthyroidism because of the presence of which of the following?

(A) Lymphoid infiltration
(B) Colloid within the follicles
(C) Parathyroid gland
(D) Parafollicular cells
(E) Cuboidal follicular cells

3. A 51-year-old man underwent surgery for removal of a carcinoma on his trachea. After surgery, he suffered excessive nervousness, muscle cramps, and spasmodic skeletal muscle contractions in his arms, legs, and feet. Laboratory tests revealed markedly low levels of calcium in his blood. Treatment with intravenous calcium and vitamin D led to recovery in a few weeks. Which condition is responsible for these symptoms in this patient following surgery?

(A) Hypothyroidism
(B) Hyperthyroidism
(C) Hypoparathyroidism
(D) Graves disease
(E) Hyperparathyroidism

Questions 4 and 5 are related to the following clinical scenario:

A middle-aged male patient sees his physician complaining about an increased level of anxiety, unusual irritability, and depression as well as thinning hair and having an inordinate amount of colds and infections. Upon examination, the physician notes that the patient, whose blood pressure was always normal in the past, is hypertensive, has developed a "buffalo hump," and has acquired a "moon-shaped" face.

4. What should the physician suspect concerning the diagnosis?

(A) Hyperthyroidism
(B) Addison disease
(C) Graves disease
(D) Cushing disease
(E) Excess growth hormone intake

5. Which region of the patient should be observed with a magnetic resonance imaging?

(A) Abdomen
(B) Pelvis
(C) Neck
(D) Thorax
(E) Head

6. Pheochromocytoma is a tumor of which organ?

(A) Pineal body
(B) Adrenal medulla
(C) Adrenal cortex
(D) Thyroid gland
(E) Parathyroid gland

7. Systemic infection by *N. meningitidis* can cause uncontrollable bleeding in which endocrine structure?

(A) Pars distalis
(B) Pars nervosa
(C) Pars intermedia
(D) Adrenal cortex
(E) Adrenal medulla

8. What is characteristic of pinealocytes?

(A) They produce melatonin.
(B) They resemble astrocytes.
(C) They contain calcified concretions of unknown function.
(D) They act as postganglionic sympathetic cells.
(E) They are unaffected by dark and light cycles.

9. Prolactin is synthesized and secreted by which of the following cells?

(A) Acidophils in the pars distalis
(B) Basophils in the pars tuberalis
(C) Somatotrophs in the pars distalis
(D) Basophils in the pars intermedia
(E) Gonadotrophs in the pars distalis

Question 10 is based on the photomicrograph below.

10. The hormone produced and released by the cell at the tip of the arrow binds to receptors on the surface of which of the following cells?

(A) Chondroblasts
(B) Osteoblasts
(C) Chondrocytes
(D) Osteocytes
(E) Osteoclasts

Answers and Explanations

1. **D.** Graves disease (exophthalmic goiter) results in an enlarged thyroid gland because of stimulation of the follicular cells to produce an excessive amount of thyroid hormones by binding of autoimmune antibodies to TSH receptors. Follicular cells actively remove colloid from the lumen of the follicles. Heat intolerance and weight loss are common, but the disease is not caused by iodine deficiency.
2. **A.** Most individuals who present with sporadic nonautoimmune hyperthyroidism possess enlarged thyroids but the histology of their thyroid glands differs from those with Graves disease because of the absence of lymphoid infiltration. One of the characteristics of the thyroid glands of individuals with Graves disease is the presence of lymphoid infiltration.
3. **C.** Upon removal of the carcinoma from his neck, the parathyroid glands were also removed or damaged, causing hypoparathyroidism (a lack of PTH, which increases blood calcium). Treatment with calcium (and vitamin D, which aids in its absorption) corrected these symptoms. The marked neuromuscular irritability in the absence of calcium reveals its importance in regulating skeletal muscle contraction.
4. **D**. Patients with Cushing syndrome exhibit fat accumulation above the clavicles, in the back of the neck (buffalo hump), the trunk, and the face (moon face, which is characteristic of this disease). Additional symptoms include being infection-prone, edema, hypertension, diabetes, troubles with wound healing, thinning of hair, irritability, anxiety, depression, and even the possibility of psychosis.
5. **E.** Because the adenomas of the pituitary gland are derived from hormone-producing parenchymal cells, they will produce an excess of the hormone or hormones that the normal cells produce. An example of such overproduction of hormone is Cushing disease, in which an excess amount of ACTH is produced, resulting in the release of an overabundance of cortisol (as well as, to some extent, aldosterone and androgens) by the suprarenal glands.
6. **B.** A pheochromocytoma is a tumor arising in catecholamine-secreting chromaffin cells of the adrenal medulla. The tumor is rare, it is found in both sexes, and 90% of the time it is benign.
7. **D.** Waterhouse–Friderichsen syndrome (hemorrhagic adrenalitis) is a very serious condition in which uncontrolled bleeding into the adrenal cortices of both adrenal glands causes them to become necrotic. The underlying cause of the condition is due to a very severe bacterial (or occasionally, viral) infection with any of the following organisms: *N. meningitidis*, *S. pneumoniae*, *H. influenzae*, or *P. aeruginosa*. Recent studies of the effects of Ebola virus indicate that infections with this virus can also be responsible for this condition.
8. **A.** Pinealocytes, the parenchymal cells of the pineal gland, produce melatonin at night and serotonin during the day. The pineal gland also contains neuroglial cells that resemble astrocytes, and its interstitium has calcified concretions called brain sand.
9. **A.** Prolactin is produced by mammotrophs, one of the two types of acidophils located in the pars distalis of the pituitary gland. As their name implies, these cells produce a hormone that regulates the development of the mammary gland during pregnancy and lactation.
10. **E.** The cell at the tip of the pointer is a parafollicular cell (clear cell) of the thyroid gland and it manufactures and releases the hormone calcitonin, which binds to calcitonin receptors on osteoclast surface, inhibiting the osteoclast from resorbing bone.

chapter 12

Skin

I. OVERVIEW—THE SKIN

The skin, the heaviest organ (about 16% of the total body weight), is composed of two layers: the **epidermis** and **dermis**, which interdigitate in the form of an irregular contour.

A. **The skin contains several epidermal derivatives (sweat glands, hair follicles, sebaceous glands, nails; also the mammary glands, which are discussed in Chapter 17).** The skin along with its derivatives is called the **integument**.

B. **The skin protects the body against injury, desiccation, and infection; regulates body temperature; absorbs ultraviolet (UV) radiation, which is necessary for synthesis of vitamin D; and contains receptors for touch, temperature, and pain stimuli from the external environment.** Additionally, skin acts as an excretory organ via sebaceous, sweat, and apocrine glands.

C. **A deeper superficial fascial layer, the *hypodermis*, lies under the skin.** This layer, which is ***not*** considered part of the skin, consists of loose connective tissue that binds skin loosely to the subjacent tissue.

II. EPIDERMIS

A. Overview—Epidermis

1. The epidermis is the **superficial layer** of the skin. Primarily of **ectodermal origin**, it is classified as **stratified squamous keratinized epithelium**. The epidermis is composed predominantly of **keratinocytes** and three other types of cells: **melanocytes**, **Langerhans cells**, and **Merkel cells**.
2. **Regeneration**, which occurs approximately every 30 days in the epidermis, is carried out by the mitotic activity of the deeper layers of keratinocytes, which normally divide only at night.
3. Deep downgrowths of the epidermis, called **epidermal ridges**, **interdigitate** with projections of the dermis (**dermal ridges**), resulting in a highly irregular interface. Each dermal ridge is often further subdivided into two secondary dermal ridges by a narrow downgrowth of the epidermis, called an **interpapillary peg**. Where the epidermis overlies the dermal ridges, surface ridges are produced. On the fingertips, these surface ridges are visible as **fingerprints**, whose configuration is genetically determined and thus unique to each individual.
4. Keratinocytes manufacture and release various signaling molecules, such as interleukins, interferons, tumor necrosis factors, and colony-stimulating factors that stimulate the immune system.

B. Layers of the epidermis (Fig. 12.1, Table 12.1)

1. The **stratum basale** (**stratum germinativum**) is the **deepest layer** of the epidermis and is composed mostly of keratinocytes that are cuboidal to columnar in shape. These **mitotically active** cells are attached directly to the basal lamina of the basement membrane by **hemidesmosomes** and to

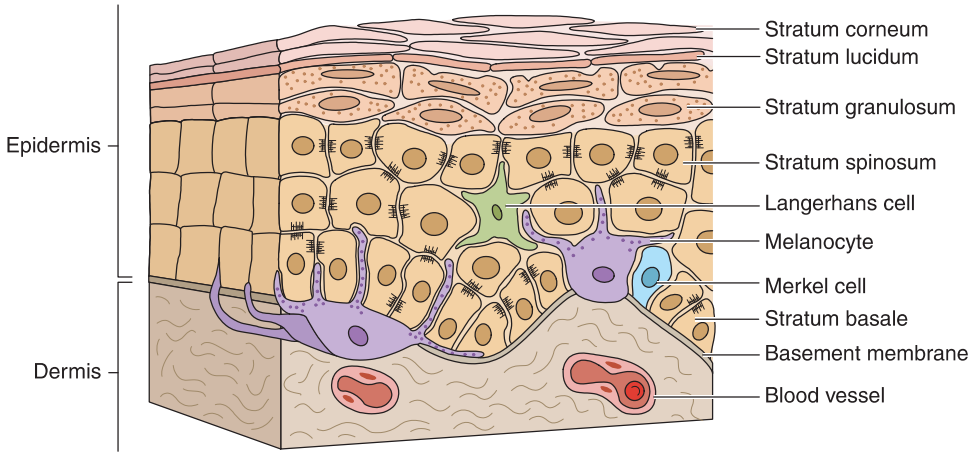


FIGURE 12.1. Layers of epidermis. The stratum lucidum is present only in thick skin and is best observed in skin from the palms of the hands and the soles of the feet. Melanocytes lie between keratinocytes in the stratum basale. (Adapted with permission from Ham AH, Cormack DH. *Histology*. 8th ed. Philadelphia, PA: Lippincott; 1979:625.)

table 12.1 Histologic Features of skin

Divisions	Layers	Characteristics
Epidermis*	Stratum corneum	The most superficial layer of epidermis Many flattened dead "cells" called squames, packed with keratin filaments Surface cells are sloughed
	Stratum lucidum	Indistinct homogeneous layer of keratinocytes; present only in thick skin Cells lack nuclei and organelles Cytoplasm is packed with keratin filaments and eleidin
	Stratum granulosum	Flattened nucleated keratinocytes arranged in 3–5 layers Cells contain many coarse keratohyalin granules associated with tonofilaments Membrane-coating (waterproofing) granules occasionally present Present only in thick skin
	Stratum spinosum	Several layers of keratinocytes, called prickle cells because they appear spiny Desmosomes, associated with tonofilaments, connect cells between processes (intercellular bridges) Keratinocytes contain membrane-coating (waterproofing) granules Keratinocytes are mitotically active, especially in deeper layers Langerhans cells are also present in this layer
	Stratum basale (stratum germinativum)	Deepest layer of epidermis, composed of a single layer of tall cuboidal keratinocytes Keratinocytes are mitotically active Melanocytes and Merkel cells are also present in this layer
Dermis†	Papillary layer	Superficial thin layer of connective tissue that interdigitates with epidermal ridges of the epidermis Forms dermal papillae where Meissner corpuscles and capillary loops may be found Contains delicate collagen (type I and type III) fibers Contains anchoring fibrils (type VII collagen), microfibrils (fibrillin), and elastic fibers
	Reticular layer	Extensive part of the dermis, lying deep to the papillary layer Contains thick bundles of collagen (type I) fibers and elastic fibers Arteries, veins, and lymphatics are present Location of sweat glands and their ducts, Pacinian corpuscles, and nerves In thin skin, contains hair follicles, sebaceous glands, and arrector pili muscles

*Stratified squamous keratinized epithelium.
†Dense, irregular connective tissue.

each other by desmosomes. These cells manufacture and contain **keratins 5 and 14**. Dispersed among the keratinocytes of the stratum basale are **melanocytes** and **Merkel cells**.

2. The **stratum spinosum** consists of a few layers of polyhedral keratinocytes (**prickle cells**). Their cytoplasmic extensions, termed "intercellular bridges" by early histologists, are now known to terminate in **desmosomes** that help these cells to adhere to each other and to the cells of the

stratum basale and stratum granulosum. Keratinocytes in the deeper aspects of the stratum spinosum are also **mitotically active**. This layer also houses **Langerhans cells**.

a. In the superficial regions of the stratum spinosum:

(1) Keratinocytes contain **membrane-coating granules** (**Odland bodies**, **lamellar bodies**) whose contents are rich in lipids, especially glycosphingolipids, ceramides, and phospholipids. The lipid contents of some of these granules are released into the intercellular spaces in the form of lipid-containing sheets that are **impermeable to water** and **many foreign substances**.

(2) They form the **intermediate filaments** composed of **keratin 1** and **keratin 10**, replacing the keratin types located in the cells of the stratum basale. These new keratins form *thin* bundles of intermediate filaments, known as **tonofilaments**.

(3) They also form nonmembrane-bound structures, known as **keratohyalin granules**, whose main components are the proteins **filaggrin** and **tricohyalin**. The keratohyalin granules envelop the thin bundles of tonofilaments, causing them to become cross-linked, thereby forming *thick* bundles of **tonofibrils**.

b. The **malpighian layer** (stratum malpighii) consists of the stratum spinosum and stratum basale. Nearly all of the mitotic activity in the epidermis occurs in this region, and cell division occurs only at night. Interleukin-1 and epidermal growth factor are thought to facilitate, whereas transforming growth factor suppresses, the mitotic activity of these cells.

CLINICAL CONSIDERATIONS

UV radiation is now known to be responsible for all three major skin cancers, basal cell carcinoma (80% of nonmelanoma skin cancers); squamous cell carcinoma (20% of nonmelanoma skin cancers); and most probably, melanoma. Annually, most of the 2,300 deaths from nonmelanoma cancers are due to squamous cell carcinoma. The sun's UV rays reach the earth as a continuous wavelength, although, customarily, for the purposes of dermatologic studies, it is described as if it were composed of three discontinuous waves of differing lengths, in which UVA is the longest (320–400 nm), UVC is the shortest (<290 nm), and UVB occupies a band of intermediate length (290–320 nm). The major component of the sun's rays (about 95%) is the UVA band (320–400 nm), and this is the component believed to be most culpable in cancer, because not only does it have the ability to penetrate to the deepest layer of the skin, but it is also the most constant component of the sun's UV radiation, irrespective of the time of the year, and passes undiminished through clouds and glass. Although UVB radiation also penetrates all layers of the skin and causes all three types of skin cancer, it is unable to penetrate glass, and its intensity varies with the time of day (strongest between 10 AM and 4 PM and only during late spring, summer, and early autumn). Most of the damage caused by UVB rays is restricted to the more superficial layers of skin. UVC radiation is unable to penetrate the ozone layer surrounding the earth and is not considered to have any biologic effect. In addition to the cancer-producing effects of UVA and UVB radiations, they also cause a condition known as "photoaging," namely, acceleration in the wrinkling and loss of elasticity of skin.

Sunscreen with a sun protection factor (SPF) rating of 15 or higher may protect against UVB wavelengths, which cause sunburn, but offers no protection against the longer UVA wavelengths. To get the best protection, use sunscreens, such as those approved by the US Food and Drug Administration (octocrylene, titanium dioxide, and zinc oxide), that shield the skin from damage from both UVA and UVB.

3. The **stratum granulosum** is the most superficial layer of the epidermis in which the cells are still alive. It comprises three to five layers of flattened keratinocytes that contain even more and bigger accumulations of **keratohyalin granules**, **thick bundles of keratin filaments** (**tonofibrils**), and **membrane-coating granules**.

a. The cytoplasmic aspect of the plasma membrane of keratinocytes in the stratum granulosum is reinforced by an electron-dense layer 10 to 12 nm thick. **Keratohyalin granules** stain intensely with basophilic stains, thus are very pronounced in histologic sections.

b. Cells in the superficial layers of the stratum granulosum form **tight junctions** with one another and with the cells of the stratum lucidum in thick skin and with cells of the stratum corneum in thin skin. These tight junctions are rich in the transmembrane protein **claudin**.

c. The lipid contents of the membrane-coating granules are released into the extracellular space to form a water-impermeable barrier preventing nutrients from reaching the superficial-most layer of cells of the stratum granulosum and those of the strata lucidum and corneum. Therefore, those cells undergo apoptosis, their organelles die, and the cells become **keratohyalin-to-nofibril–filled** "hulls." The impermeable layer also prevents aqueous fluid from entering the epidermal layers from the external environment.

4. The **stratum lucidum** is a clear, homogeneous layer just superficial to the stratum granulosum; it is often difficult to distinguish in histologic sections. It is found only in **palmar** and **plantar skin**. This layer consists of keratinocytes that have neither nuclei nor organelles but contain an abundance of tonofibrils embedded in keratohyalin, frequently referred to as **eleidin**. The nonkeratin-based protein **involucrin** reinforces the internal aspect of the plasmalemmae of these cells.
5. The **stratum corneum** is the most **superficial layer** of the epidermis (Fig. 12.2). It may consist of as many as 15 to 20 layers of flattened, nonnucleated dead "cells" filled with **keratohyalin–keratin**

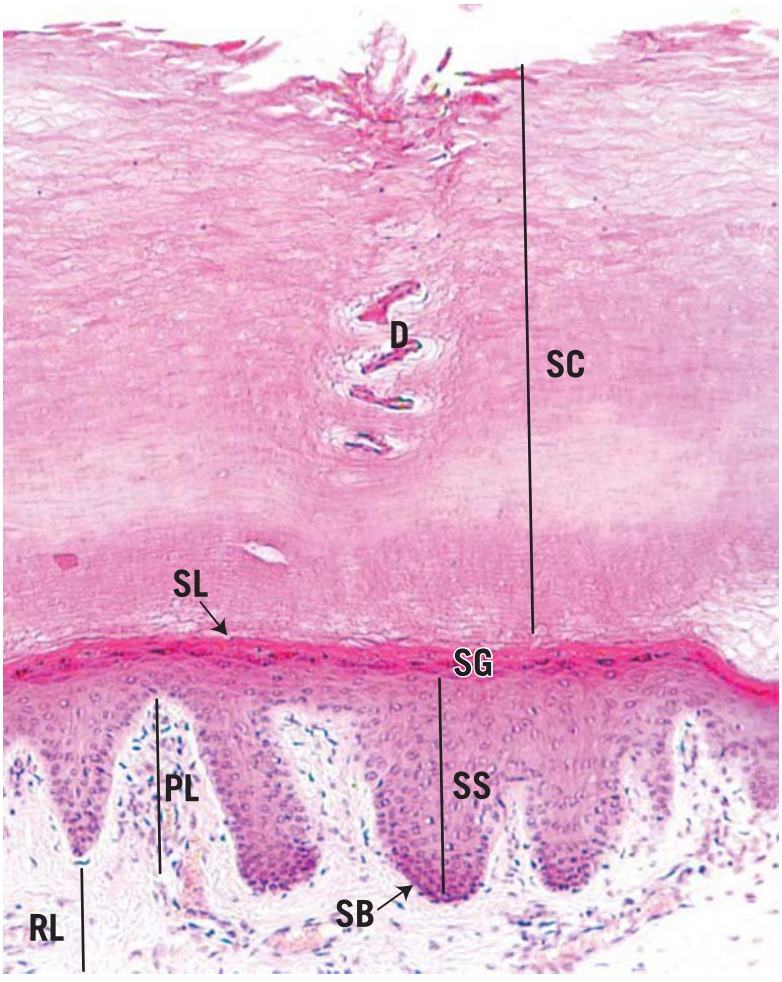


FIGURE 12.2. This is a photomicrograph of thick skin from a human palm. Note the sweat gland duct (D) in the middle of the image as it courses in a corkscrew fashion through the very thick stratum corneum (SC). The thin stratum lucidum (SL) is situated between the SC and the stratum granulosum (SG). The thick stratum spinosum (SS) and the single-layered stratum basale (SB) constitute the remainder of the epidermis. The dermis is composed of two layers, the narrow papillary layer (PL) that interdigitates with the epidermis and the very thick reticular layer (RL) whose entire extent is not shown in this photomicrograph (×270).

complex. These **nonviable scale-like** structures are called **squames** (or horny cells) and have the shape of a flat 14-sided polygon.

- **a.** The keratohyalin–keratin complex lines the plasma membrane of the stratum corneum cell and is further fortified by three proteins: **involucrin**, **small proline-rich protein**, and **loricrin**, thereby establishing a thickened **cornified cell envelope**.
- **b.** The lipid-rich substance released from the membrane-coating granules in the strata spinosum and granulosum into the extracellular space coats the cells of the stratum corneum, forming a **lipid coat** around each cell.
- **c.** The cornified envelope in conjunction with the lipid coat constitutes the **compound-cornified cell envelope**.

6. The outermost layer of squames is continuously shed by **desquamation**. The rate of shedding matches the rate of cell renewal in the strata basale and the spinosum, thereby maintaining the thickness of the epidermis as well as the structural stability of the compound-cornified cell envelope.

CLINICAL CONSIDERATIONS

Psoriasis vulgaris (**plaque psoriasis**), a condition in which reddened, inflamed patches of skin, having a whitish, flaky layer on top, appear almost anywhere on the body, is the most common form of psoriasis. It is the result of an increase in the mitotic activity and a decreased duration of the cell cycle of the cells in the malpighian layer of the epidermis (stratum basale and stratum spinosum); the epidermis is often renewed in only days rather than in about a month. The fast-growing epidermis promotes increased blood flow to nourish the accelerated growth, and inflammation may occur (both causing redness). Males and females have an equal incidence of the condition. Psoriasis has a genetic component with several genes (*PSORS1* through *PSORS9*, with *PSORS1* the most closely associated gene) that were identified as being linked to the condition; in fact, about 30% of the patients present with a family history. The development of psoriasis appears to have an immune factor, in that antigen-presenting cells induce the development of T helper cells (T_H1 and T_H17) along with the presence of a number of cytokines, including IL-12, IL-23, interferon-γ, and tumor necrosis factor-α. Interestingly, psoriasis may also involve the nails, which become thick and pitted in appearance and, frequently, yellowish lesions are visible beneath the nail plate.

C. Nonkeratinocytes in the epidermis: melanocytes, Langerhans cells, and Merkel cells (Table 12.2)

1. **Melanocytes** (Fig. 12.1) are present in the **stratum basale** and originate as melanoblasts from neural crest. Once melanoblasts reach the epidermis they become **premelanocytes**, enter the stratum basale, form hemidesmosomes with the basal lamina but do not form adhesive junctions with the keratinocytes. Once premelanocytes bind **stem cell factor** they may remain premelanocytes or may differentiate into melanocytes, which extend fingerlike processes known as **dendrites** that occupy some of the extracellular spaces among the cells of the stratum spinosum. The dendrites of a single melanocyte contact a number of stratum spinosum cells and this group of cells is known as an **epidermal-melanin unit**.

- **a.** Melanocytes synthesize **melanin** in organelles known as **melanosomes** under the influence of the pituitary hormone, **melanocyte-stimulating hormone** (**MSH**). MSH acts by binding to receptors, specifically **melanocortin 1 receptors** (**MC1R**) on the melanocyte plasma membrane, which causes these cells to activate their **microphthalmia-associated transcription factor**, a signaling molecule that induces melanin synthesis by the UV-sensitive enzyme,

table **12.2** Nonkeratinocytes of the Epidermis

Cell	Location	Derivation	% of Epidermal Cells	Function
Melanocyte	Stratum basale	Neural crest cells	2–3	Synthesis of melanin
Langerhans cell	Stratum spinosum	Bone marrow	2–4	Antigen presentation
Merkel cell	Stratum basale	Neural crest cells; perhaps epidermis	1–5	Mechanoreceptors

tyrosinase. Additionally, these receptors also induce melanocytes to enter the cell cycle. Moreover, MSH binding to MC1R induces pathways that repair deoxyribonucleic acid (DNA) and antioxidant formation. The two types of melanin produced by melanocytes are eumelanin and pheomelanin.

(1) **Eumelanin** (or just **melanin** in this textbook) has two major varieties, brown and black. These are both dark and impart a dark coloration to skin. With age, only the black form of melanin is produced. Melanin is produced in oval-shaped organelles, known as melanosomes. Melanin is photoprotective (i.e., it absorbs UV radiation and protects the DNA of epidermal cells from damage).

(2) **Pheomelanin** is reddish to yellow in color, and this form of melanin gives skin a slightly pinkish coloration. Pheomelanin is produced in spherical organelles, also known as melanosomes. Pheomelanin does not offer the same protection against DNA damage as does melanin.

(3) Mature melanin-containing melanosomes are transported into the dendrites along microtubule pathways, powered by **myosin Va**, and at the proper location the melanosomes are transferred to **F-actin** pathways that deliver them to the dendrite's plasma membrane where the melanosomes are released into the extracellular space.

b. Cells of the stratum spinosum phagocytose the released melanosomes (Fig. 12.3). Once inside the keratinocytes the melanosomes migrate to the region of the nucleus and form a **physical barrier** between the keratinocyte's nucleus and the impinging UV rays of the sun, thus protecting the keratinocyte's chromosomes from possible damage from the UV radiation.

(1) The number of melanocytes per unit area of skin appears to be the same in dark- and light-skinned people and account for approximately 3% of the entire epidermal cell population.

(2) Pigmentation differences are due to the rate of melanin synthesis, melanosome size, content, rate of transfer, and degradation patterns.

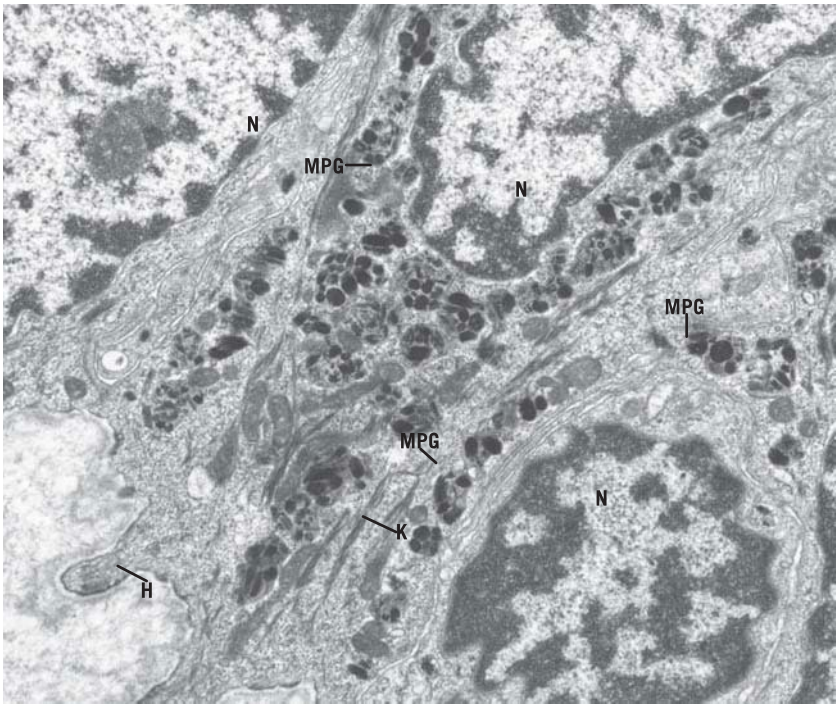


FIGURE 12.3. An electron micrograph of keratinocytes in the stratum basale of skin. Melanin pigment granules (MPG) are abundant in the cytoplasm, having been transferred to the cells via melanocyte processes. A few keratin filaments (K), mitochondria, and portions of nuclei (N) are observed. The base of keratinocytes in this layer attaches to the basal lamina by hemidesmosomes (H), and they attach to neighboring cells by way of desmosomes (×9,500).

CLINICAL CONSIDERATIONS

Melanoma is a form of skin cancer that can be life-threatening, if it is not treated early enough to prevent its metastasis. It originates in melanocytes, cells located in the stratum basale, and has specific characteristics that should be recognized by all practitioners of family medicine, as they are the most likely to encounter these lesions. The early signs of melanoma include alterations of an existing mole that may, but not necessarily, include painful, itching, or burning sensations reported by the patient. The color of the lesion varies from black to brown to blue to occasionally even pink. Any pigmented lesion that has changed color; is asymmetric with irregular borders; and has increased in size, especially becoming greater than 6 mm in diameter (the diameter of a pencil eraser), should be considered suspicious. Melanomas can occur almost anywhere on the body, but most commonly in areas that are exposed to sunlight, although melanomas of the rectoanal, vulvar, and mucosal regions as well as urogenital tract also occur. Another possible site for melanoma is the uvea of the eye.

Approximately 86% of melanomas are believed to be caused by exposure to UV radiation from the sun. Although malignant melanoma accounts for less than 5% of skin cancer cases, it is responsible for the vast majority of skin cancer deaths.

The incidence of malignant melanoma is rapidly increasing in the United States. According to the National Cancer Institute, 87,000 new cases of malignant melanoma resulting in more than 9,730 fatalities were reported in the United States in 2017.

Single-nucleotide polymorphism in the gene coding for the MC1R receptor is responsible for the formation of loss-of-function MSH receptor, which results in the synthesis of pheomelanin and the lack of induction of DNA repair and antioxidant-forming pathways. Absence of these two pathways is a major contributor to an increase in the incidence of melanoma.

2. **Langerhans cells** (**dendritic cells**, so named because of their long processes) originate in the bone marrow and travel in the bloodstream to enter the dermis from which they migrate into the epidermis to become localized primarily in the **stratum spinosum**. These independent cells make no adhesive junctions with keratinocytes; they contain characteristic paddle-shaped **Birbeck granules** that possess the lectin receptor protein, **langerin**, in their membrane.
   a. Langerhans cells also express, on their plasmalemmae, various immune-related proteins, namely, CD1a; MHC I and MHC II; and C3b receptors, as well as receptors for IgG. The protein **CD1a**, in association with **langerin** in the Birbeck granule membrane, defends the organism against the causative agent of leprosy, *Mycobacterium leprae*.
   b. Langerhans cells function as **antigen-presenting cells** in immune responses to **contact antigens** (**contact allergies**) and some skin grafts. Once Langerhans cells phagocytose antigens, these foreign proteins are engulfed by the Birbeck granule where they are processed into epitopes, and Langerhans cells leave the epidermis, travel to a lymph node, and there they will present the epitope to T cells and thereby initiating a **delayed-type hypersensitivity reaction**.
3. **Merkel cells** are present in small numbers in the **stratum basale,** near areas of well-vascularized, richly innervated connective tissue.
   a. They are believed to be of neural crest cell in origin, but as they possess desmosomes and keratin filaments, an epidermal origin has also been suggested.
   b. Their pale cytoplasm contains **small**, **dense-cored granules** that are similar in appearance to those in some cells of the diffuse neuroendocrine system and are presumed to house neurosecretory products.
   c. They receive afferent nerve terminals of myelinated sensory nerves that form **Merkel cell–neurite complexes** that probably function as **mechanoreceptors**. They appear to be more abundant in areas of acute sensory perception, as at the tips of fingers.

D. Thick and thin skin **are distinguished on the basis of the *thickness of the epidermis*.**

1. **Thick skin** has an epidermis that is **400 to 600 μm thick** and is characterized by a prominent stratum corneum, a well-developed stratum granulosum, and often a distinct stratum lucidum. It lines the palms of the hands and the soles of the feet; therefore, it **lacks** hair follicles, sebaceous glands, and arrector pili muscles.

2. **Thin skin** has an epidermis that is **75 to 150 μm thick**, has a less prominent stratum corneum than thick skin and generally lacks both a stratum granulosum and stratum lucidum, although it contains individual cells that are similar to the cells of these layers. Thin skin covers most of the body and contains hair follicles, sebaceous glands, and arrector pili muscles.

CLINICAL CONSIDERATIONS

Epidermolysis bullosa (**EB**) is a group of **hereditary** diseases of the skin characterized by **blister formation** following minor trauma to the skin. These diseases are caused by **defects in the keratinocyte intermediate filaments** that provide mechanical stability and in the **anchoring fibrils** that attach the epidermis to the dermis. The four major types of EB are EB simplex, junctional EB, dystrophic EB, and EB acquisita. They vary in the degree of severity and the locus of the genetic defect. Over 90% of EB is of the **EB simplex** type, in which the genetic defect occurs in the genes for keratin 5 and keratin 14. In this condition, the blistering occurs in the region of trauma, namely on the hands and feet. The second most prevalent form is **dystrophic EB** (about 5% of the cases) in which the genetic defect involves type VII collagen that forms the anchoring fibrils. The number of anchoring fibrils is greatly reduced and results in numerous blisters throughout not only the skin but also in the epithelial lining of the esophagus. The skin and esophagus of affected individuals display severe scarring resulting from infections and lack of adequate healing. Many dystrophic EB patients develop squamous cell carcinoma, which is one of the principal causes of death prior to age 30.

III. DERMIS

The **dermis** is the connective tissue layer of the skin that underlies the epidermis. It is of **mesodermal origin** and is composed of dense, irregular connective tissue that contains many **type I collagen fibers** and networks of thick **elastic fibers**. Although it is divided into a **superficial papillary layer** and a **deeper**, more extensive **reticular layer**, no distinct boundary exists between these layers (Table 12.1).

A. **The dermal papillary layer is uneven (Fig. 12.2) and forms *dermal ridges* (*dermal papillae*), which interdigitate with the epidermal downgrowths (epidermal ridges) forming the epidermal/dermal junction.** The papillary layer is composed of thin, loosely arranged connective tissue containing fibroblasts, type III collagen fibers, fine elastic fibers, and capillary loops. Also located in the papillary layer are **Meissner corpuscles**, fine-touch receptors that make it possible to specifically identify two different coins in your pocket simply by feeling them. Fine, unmyelinated nerve fibers course through the papillary layer to gain access to the extracellular spaces of the epidermis where they function as pain receptors.

B. **The deeper dermal reticular layer constitutes the major portion of the dermis.** It is composed of dense bundles of **type I collagen fibers** and thick **elastic fibers**. In its deeper aspects, it may contain **Pacinian corpuscles** (Fig. 12.4), which are pressure receptors, as well as **Krause end-bulbs** (formerly thought to be cold receptors, but their actual function is uncertain). Specialized diffuse receptors are discussed in Chapter 19.

C. **Located at various levels in the dermis are the appendages of the skin.** These include the two types of sweat glands (eccrine and apocrine), sebaceous glands, hair follicles, and nails.

CLINICAL CONSIDERATIONS

Keloids (abnormal scar tissue) are swellings in the skin that result from increased collagen formation in hyperplastic scar tissue. Most affected by keloid formation are humans of 10 to 30 years of age, and African Americans are disproportionately affected. Keloids usually grow far beyond the actual boundary of the original lesion and, aside from their un-aesthetic appearance, can be the cause of discomfort such as itching and pain. If the keloid forms across a joint, then the patient's mobility across that joint may become reduced. Unfortunately, no single therapeutic measure can alleviate all the problems caused by the keloid; therefore, each patient's treatment has to be tailored individually. These treatments can be as extensive as surgical removal of the keloid, injection of steroids into the keloid, and cryotherapy (using liquid nitrogen) as well as laser therapy.

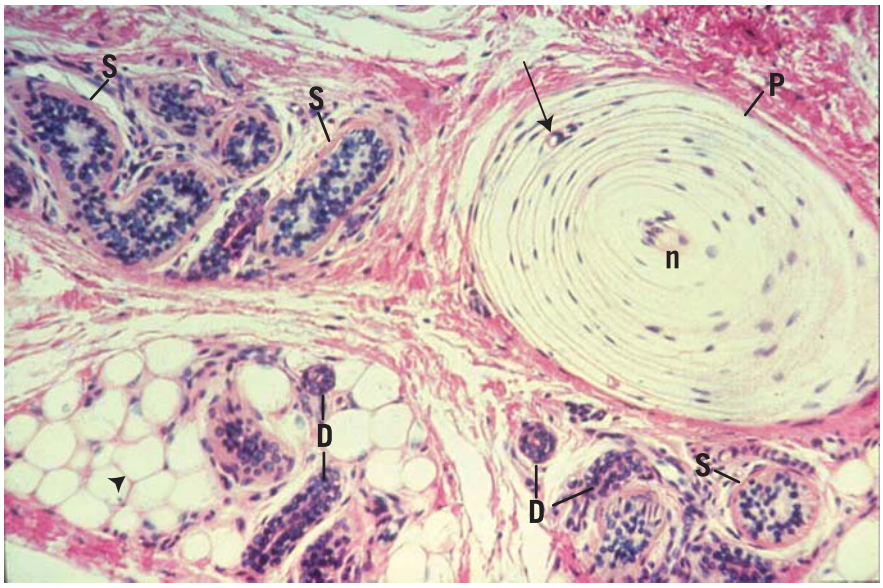
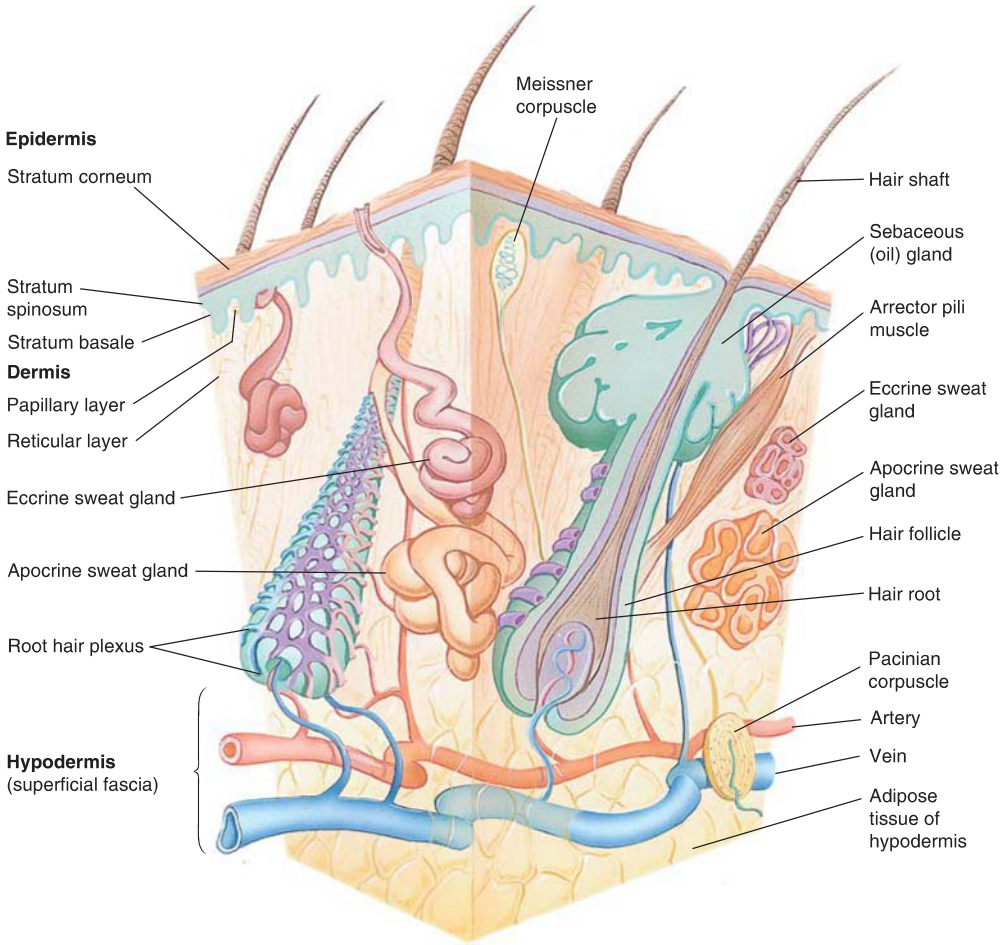


FIGURE 12.4. A light micrograph of eccrine sweat glands and a Pacinian corpuscle in the dermis of the skin. Sweat glands are also present in the hypodermis among adipose cells (*arrowhead*). The secretory units (S) of the sweat glands are wrapped by fingerlike processes of myoepithelial cells and stain more lightly than the ducts (D) that are lined by a stratified cuboidal epithelium. This Pacinian corpuscle (P) lies deep in the dermis and is composed of a centrally located nerve (n) surrounded by concentric layers of connective tissue. The nuclei of fibroblasts are seen, and so is a capillary (*arrow*), which helps to nourish the structure. Pacinian corpuscles are mechanoreceptors that respond to deep pressure (×150).

IV. GLANDS IN THE SKIN (Fig. 12.5)

A. **The 3 to 4 million eccrine sweat glands (Fig. 12.4) are *simple coiled tubular glands* consisting of a secretory unit and a single duct.** These glands are present in skin throughout most of the body but not in the lips and not in certain regions of the external genitalia. Eccrine sweat glands function in controlling body temperature, conserving electrolytes, and excreting sweat containing a low concentration of urea and lactic acid. They are stimulated by sympathetic innervation as a result of elevated body temperature.

1. The **secretory unit of eccrine sweat glands** is approximately 0.4 mm in diameter and is embedded in the dermis; it is composed of three cell types.
   a. **Dark cells** line the lumen of the gland and contain many mucinogen-rich secretory granules.
   b. **Clear cells**, which underlie the dark cells, are rich in mitochondria and glycogen and contain intercellular canaliculi that extend to the lumen of the gland. These cells secrete a watery, electrolyte-rich material.
   c. **Myoepithelial cells** lie scattered in an incomplete layer beneath the clear cells. They stain deeply with eosin and are easily identified in histologic sections. Their contractions aid in expressing the gland's secretions into the duct.
2. The **ducts** (Fig. 12.4) **of eccrine sweat glands** are **narrow** and are lined by a **stratified cuboidal epithelial epithelium**, which contains many keratin filaments and has a prominent terminal web. The cells forming the external (basal) layer of the duct have many mitochondria and a prominent nucleus.
   a. The duct leads from the secretory unit through the superficial portions of the dermis to penetrate an **interpapillary peg** of the epidermis where the duct cells end. Beginning from this point the walls of the duct are formed by epidermal cells as the duct forms a tight spiral through the layers of the epidermis to open at the surface of the skin at a **sweat pore** to deliver sweat on the skin surface (Fig. 12.2).
   b. As the secreted material passes through the dermal region of the duct, its cells reabsorb some electrolytes and excrete other substances (such as urea, lactic acid, ions, and certain drugs).



Skin and its appendages, **hair**, **sweat glands** (both **eccrine** and **apocrine**), **sebaceous glands**, and **nails**, are known as the **integument**. Skin may be **thick** or **thin**, depending on the thickness of its epidermis. Thick skin epidermis is composed of five distinct layers of **keratinocytes** (strata basale, spinosum, granulosum, lucidum, and corneum) interspersed with three additional cell types, **melanocytes**, **Merkel cells**, and **Langerhans cells**. Thin skin epidermis lacks strata granulosum and lucidum, although individual cells that constitute the absent layers are present.

FIGURE 12.5. A diagram illustrating skin and its derivatives. (From Gartner LP. *Color Atlas of Histology*. 7th ed. Baltimore, MD: Wolters Kluwer; 2018:304.)

CLINICAL CONSIDERATIONS

Hyperhidrosis is a disorder of excessive sweating caused by overperspiration from secretion by eccrine sweat glands in the skin. Treatment with drugs have been unsatisfactory in alleviating the symptoms of this condition, but injecting a highly diluted form of **Botox** directly into the skin on the palms of the hands, soles of the feet, or of the axillae offers relief. The toxin blocks sympathetic nerve impulses to the cells of the eccrine sweat glands and decreases their ability to secrete. A single injection of Botox may provide months of relief, and the injections can be repeated when excessive sweating resumes.

B. **Apocrine sweat glands (Fig. 12.5) include the *large, specialized sweat glands*, approximately 3 mm in diameter, located in various areas of the body (e.g., axilla, areola of the nipple, perianal region) and the ceruminous (wax) glands of the external auditory canal.** Apocrine glands are stimulated by sympathetic innervation usually in response to stressful conditions.

1. These glands do not begin to function until puberty and are **responsive to hormonal influences**; their large coiled secretory units are located in the dermis and hypodermis and are enveloped by scattered myoepithelial cells. Unlike in eccrine glands, the secretory units are composed of a single cell type. These glands empty their viscous, odorless secretions into hair follicles at a

location superficial to the entry of sebaceous gland ducts. Bacteria act on these secretions to produce odors that are somewhat specific to each individual.

2. Although the term **apocrine** implies that a portion of the cytoplasm becomes part of the secretion, electron micrographs have shown that the **cytoplasm does not become part of the secretions** of apocrine sweat glands.

CLINICAL CONSIDERATIONS

Axillary osmidrosis (**axillary body odor**) is caused by the action of bacteria on fatty acid-, androstenone- and androstenol-containing secretions of the **apocrine glands**. Each individual has a distinctive odor that is so characteristic that parents can recognize their biologic children and babies can recognize their mothers by these olfactory cues. A particular gene, *ABCC11* gene, originally recognized to code for multidrug resistance protein 8, is now known to transport small molecules into and out of cells. People who present with a **single nonsynonymous nucleotide polymorphism** of this gene from both parents (namely, the **AA allele**), that is, a point mutation in which a single guanine nucleotide is changed to an adenine, have no body odor and have dry earwax. Individuals with all other alleles, GA and GG, have wet earwax and body odor. The AA allele is widespread among Koreans and many nationalities in East Asia but is totally absent in Africans, African Americans, and most Caucasians.

C. Sebaceous glands **(Fig. 12.5) are *branched acinar holocrine glands* that exhibit a lobular appearance. Clustered acini of one sebaceous gland empty into a single short duct, which delivers the secretion into the neck of the hair follicle.**

1. Sebaceous glands are embedded in the dermis over most of the body's surface but are absent from the palms and soles. They are most abundant on the face, forehead, and scalp, and they release **sebum** (composed of an oily secretion and degenerating epithelial cells). As sebum is continued to be produced, the cell undergoes apoptosis and/or necrosis, thus the cellular debris becomes a component of the secretory product.
2. Sebum has a number of functions, including the maintenance of the skin's barrier to aqueous fluids, guarding skin from oxidative stress, shielding skin from microorganisms, and maintaining the suppleness of skin and the luster of hair.

V. HAIR, HAIR FOLLICLE, AND ARRECTOR PILI MUSCLE (Figs. 12.5 and 12.6)

A. Hairs (hair shafts), **one of the characteristics of mammals, are keratinized, thin, threadlike structures that extend for various lengths above the surface of the epidermis.** Hair in mammals functions in thermal protection and in some instances as camouflage and sensory organ, whereas in humans its function is more of a tactile sensory organ because when a hair shaft is disturbed it transduces that sensory information to the nervous system. The three types of human hairs include one of which is present prenatally and gone shortly after birth, known as the lanugo, and two that are present postnatally, known as vellus hairs and terminal hairs.

1. **Lanugo** is an exceptionally fine, somewhat longish hair that covers almost the entire fetus and falls out shortly after birth.
2. **Vellus hairs** are present throughout the individual's life. They are almost invisible, but when viewed in sunlight at an angle, for instance on a person's eyelids (on the skin of the eyelids not the eyelashes), they are evident as short, very fine, soft, and pale structures. Most of the human body is covered by vellus hairs.
3. **Terminal hairs** are the coarse, long, highly keratinized, dark hairs that one associates with the word "hair." These are present on the head, eyebrows, eyelashes, groin, and so on. Most of the primate body is covered by terminal hair.

B. A hair follicle **is an *invagination of the epidermis* extending deep into the dermis.**

1. The **hair shaft** is a long, slender filament in the center of the follicle that extends above the surface of the epidermis. It consists of an inner **medulla**, **cortex**, and **cuticle of the hair**. At its deep end, it is continuous with the **hair root**. The cuticle of the hair is surrounded by the **internal root sheath**.

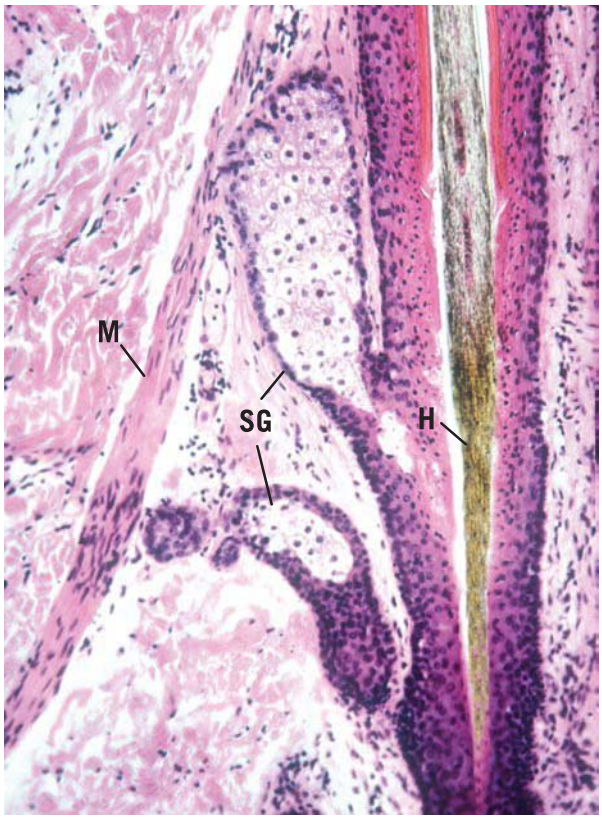


FIGURE 12.6. Light micrograph showing a portion of a hair follicle in thin skin. A hair shaft (H) is present within the follicle, and the surface of the skin is out of view at the right. Two sebaceous glands (SG) and an arrector pili muscle (M) are also observed. This muscle originates in the papillary layer of the dermis and passes obliquely to insert on the hair follicle. When it contracts, it causes the hair to stand more upright, makes the surface of the skin dimple (causing "goose flesh"), and compresses the sebaceous gland so that it expresses sebum into the shaft of the hair follicle (×50).

2. The **hair root** is the terminal expanded region of the hair follicle, located deep within the dermis where the hair is rooted. The hair root is deeply indented by a **dermal papilla**, which contains a capillary network necessary for sustaining the follicle. The hair root is separated from the dermal papilla by a basement membrane.
   - **a.** The **hair root** contains keratinocytes that function as **stem cells** for hair shaft regeneration. These stem cells are present even in bald individuals but the signaling molecules that induce them to form new hair are absent.
   - **b.** The majority of the cells of the hair root comprise the **matrix** whose cells form the **medulla** (the core of thick hairs) and the internal root sheath.
     - **(1)** The **internal root sheath** lies deep to the entrance of the sebaceous gland. It is composed of the **Henle layer**, the **Huxley layer**, and the **cuticle of the internal root sheath** (not to be confused with the cuticle of the hair).
     - **(2)** The **external root sheath** is a direct continuation of the stratum malpighii of the epidermis.
     - **(3)** The **glassy membrane**, a thickened basement membrane, separates the hair follicle from the surrounding dermal sheath.
   - **c.** **Melanocytes** are located in the matrix, lying on the basement membrane. The long dendrites of these cells penetrate the extracellular space among cells of the cortex and deliver their melanosomes into these spaces. Cells of the cortex phagocytose the melanosomes, and, in this fashion, hair acquires its color (Table 12.3).

CLINICAL CONSIDERATIONS

The production of **pheomelanin** appears to be dependent on a **loss-of-function mutation in the MC1R transmembrane molecule**. Thus, individuals with this mutation produce less melanin and more pheomelanin; therefore, their hair is reddish in color. As indicated in the Clinical Considerations discussing melanoma, individuals with this type of mutation have a greater incidence of melanoma, demonstrating a correlation between red hair and melanoma occurrence. Another interesting correlation is that the incidence of Parkinson disease is greater in people with red hair than with any other hair color.

table 12.3 Pigments that Determine Hair Color

Hair Color	High Concentration/Low Concentration of Pigment
Black	High concentration of black melanin
Brown	High concentration of brown melanin
Blonde	Low concentration of brown melanin
Red	High concentration of pheomelanin
Gray	Lack of melanin and pheomelanin
White	Very low concentration of black melanin

Note that hair color is a multifactorial trait, and the information in this table is highly simplified.

3. The average human head has approximately 150,000 hairs, which grow at an approximate rate of 2 mm/d. Hair growth occurs in three phases, a growing phase, known as the **anagen phase**; a short respite from active growth, known as the **catagen phase**; and the terminal resting phase, known as the **telogen phase**. When the hair falls out, that shed hair is known as a club hair because it possesses a club-shaped root. Approximately 50 to 100 hairs are lost from the head every day. Hairs in some regions of the body last longer than in others; hair on the head stays in place for as long as 7 years, whereas hairs in the armpit fall out in less than a half a year.

C. **The arrector pili muscle attaches at an *oblique angle to the dermal sheath* surrounding a hair follicle.** It extends superficially to underlie sebaceous glands (Fig. 12.7), passing through the reticular layer of the dermis and **inserting into the papillary layer** of the dermis. Contraction of this **smooth muscle** elevates the hair and is responsible for formation of goose bumps, caused by depressions of the skin where the muscle attaches to the papillary layer of the dermis.

VI. NAILS (Fig. 12.8)

Nails, located on the distal phalanx of each finger and toe, are hard keratinized plates that rest on the **nail bed** composed of the epidermis and underlying dermis of the skin. At the proximal end, each nail is covered by a fold of epidermis, called the **cuticle** (**eponychium**), which corresponds to the stratum corneum. The cuticle overlies the crescent-shaped whitish **lunula**. At the distal (free) edge, each nail is underlain by the **hyponychium**, which is also composed of stratum corneum. Nails grow as the result of mitoses of cells in the matrix of the **nail root**. Fingernails grow no more than 0.5 mm/wk and toenails grow a bit slower; growth is faster in the summer than in any other time of the year.

CLINICAL CONSIDERATIONS

Warts (**verrucae**), common **skin lesions** caused by a **virus**, may occur anywhere on the skin or on the oral mucosa but are most common on the dorsal surfaces of the hands, often **close to the nails**. Histologic features of warts include marked epidermal hyperplasia; eosinophilic cytoplasmic inclusions; and deeply basophilic nuclei. By electron microscopy, many intranuclear viral particles can be observed in the keratinocytes.

Male pattern baldness (**androgenic alopecia**) is a genetic condition that accounts for almost 95% of male baldness. It is recognizable by the loss of hair at both sides of the temple as well as at the crown of the head. Usually, the two patterns occur simultaneously and result in a bald top with an open ring of hair on the side and back of the head. In males, the hair loss can begin in the early 30s, but, in most men, it does not begin until the individual is in his 50s. The principal cause of male pattern baldness is the presence of **dihydrotestosterone**, the male sex hormone, which acts on the hair follicles, reducing their size and forcing them into dormancy. A similar condition, **female pattern baldness**, is also evident in women but not to the same extent as in males.

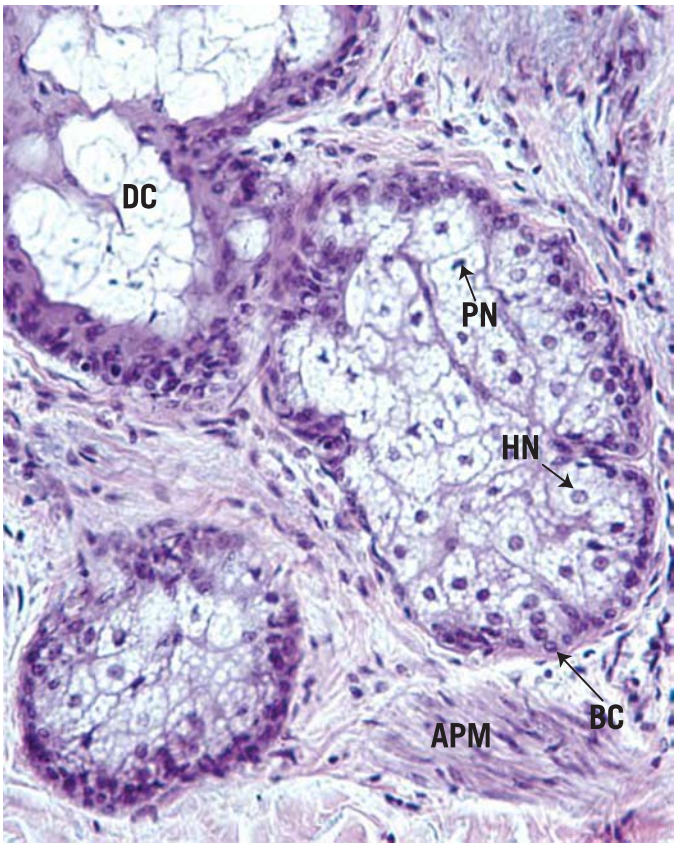


FIGURE 12.7. This high magnification of a sebaceous gland displays the basal cells (BCs) that are responsible for the regeneration of the gland. Young cells are evident because of their healthy nuclei (HN) and the dying cells display pyknotic nuclei (PN). Cells that are dead (DC) are going to be released, via holocrine secretion, into the follicular canal of the hair follicle. Observe the arrector pili muscle (APM) (×270).

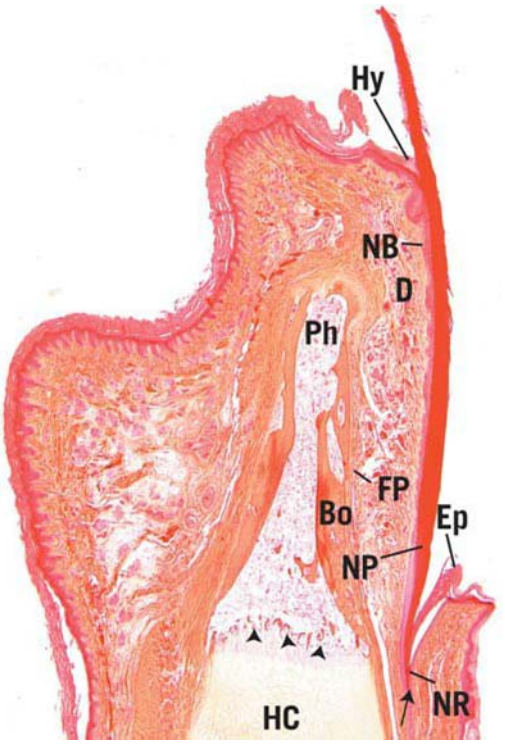


FIGURE 12.8. A fingernail on the dorsal surface of a distal phalanx (Ph) is illustrated. The highly keratinized nail plate (NP) extends deep into the dermis (D) to form the nail root (NR). The epidermis of the distal phalanx forms a continuous fold, resulting in the eponychium (Ep), or cuticle, the nail bed (NB) underlying the NP, and the hyponychium (Hy). The epithelium (*arrow*) surrounding the NR is responsible for the continuous elongation of the nail. The dermis between the NB and the bone (Bo) of the distal phalanx is tightly secured to the fibrous periosteum (FP). The presence of hyaline cartilage (HC) and endochondral osteogenesis (*arrowheads*) indicates that this is a developing finger.

Review Test

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or completions of the statement. Select the ONE lettered answer that is BEST in each case.

Questions 1, 2, and 3 refer to the following clinical scenario:

A dermatologist explains to his patient about UV radiation from the sun. He indicates that, although the sun's rays form waves that are of continuous length, for the sake of convenience, the UV rays are grouped into three groups UVA, UVB, and UVC.

1. UVC rays pose little harm to humans because they cannot penetrate which structure?

(A) Epidermis
(B) Dermis
(C) Glass
(D) Clouds
(E) Ozone layer

2. UVB rays can penetrate all of the following EXCEPT one. Which is that one exception?

(A) Epidermis
(B) Dermis
(C) Glass
(D) Clouds
(E) Ozone layer

3. According to the US Food and Drug Administration, which is the best sunscreen protection against UVA radiation?

(A) Titanium oxide
(B) Titanium dioxide
(C) Zinc chloride
(D) Zinc dichloride
(E) Sunscreen with an SPF greater than 15

4. A patient is told by his dermatologist that he has the most common type of psoriasis. What type of psoriasis does he have?

(A) Guttate psoriasis
(B) Pustular psoriasis
(C) Inverse psoriasis
(D) Psoriasis vulgaris
(E) Erythrodermic psoriasis

Questions 5 and 6 refer to the following clinical scenario:

A 35-year-old, naturally blond-haired woman is seen by her physician for an annual physical exam. Her internist notes the presence of a pigmented lesion on the back of her shoulder.

5. How large a mole should cause suspicion of a possible melanoma?

(A) 2 mm in diameter
(B) 3 mm in diameter
(C) 4 mm in diameter
(D) 5 mm in diameter
(E) 6 mm in diameter

6. Although individuals of any hair color can have melanoma, which natural hair color has a strong association with both Parkinson disease and melanoma?

(A) Blond
(B) Brunette
(C) Black
(D) Red
(E) Gray

7. A patient is seen by a dermatologist for a wart on his finger approximately 5 mm from his nail. A common histologic feature of warts is the presence of

(A) intracytoplasmic parasites.
(B) intranuclear viruses.
(C) intracytoplasmic bacteria.
(D) intranuclear yeast.
(E) intracytoplasmic fungi.

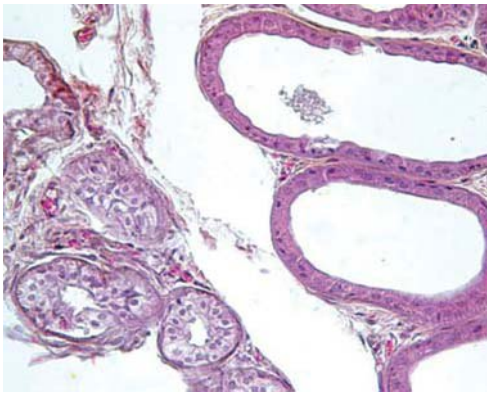
8. Which of the following statements about hair follicles is true?

(A) They are always associated with an eccrine sweat gland.
(B) They are present in thin skin but not in thick skin.
(C) Their associated arrector pili muscle is composed of striated fibers.
(D) Their hair shaft inserts into the papillary layer of the epidermis.
(E) They do not extend into the dermis.

9. Which of the following statements about eccrine sweat glands is true?

(A) They are absent in thick skin.
(B) They are holocrine glands.
(C) They have a narrow duct lined by a stratified cuboidal epithelium.
(D) They secrete an oily material called sebum.
(E) They empty into hair follicles.

Question 10 refers to the photomicrograph below.



10. This photomicrograph is a healthy region peripheral to a biopsied lymph node. From which region of the body was the biopsy obtained?

(A) Axilla
(B) Labia majora
(C) Scrotum
(D) Palm of the hand
(E) Scalp

Answers and Explanations

1. **E.** UVC radiation has the shortest wavelength and is unable to penetrate the ozone layer surrounding the earth; therefore, it cannot reach people and has no biologic effects.
2. **C.** Although UVB radiation also penetrates all layers of the skin and causes all three types of skin cancer, it is unable to penetrate glass and its intensity varies with the time of day (strongest between 10 AM and 4 PM and only during late spring, summer, and early autumn). Most of the damage caused by UVB rays is restricted to the more superficial layers of skin.
3. **B.** Sunscreen with an SPF rating of 15 or higher may protect against UVB wavelengths, which cause sunburn, but offers no protection against the longer UVA wavelengths. To get the best protection, select sunscreens, such as those approved by the US Food and Drug Administration (octocrylene, titanium dioxide, and zinc oxide), that shield the skin from damage from both UVA and UVB.
4. **D.** Psoriasis vulgaris, a condition in which reddened, inflamed patches of skin, having a whitish, flaky layer on top, appear almost anywhere on the body, is the most common form of psoriasis.
5. **E.** Any pigmented lesion that has changed color, is asymmetric with irregular borders, and has increased in size, especially becoming greater than 6 mm in diameter (the diameter of a pencil eraser), should be considered suspicious.
6. **D.** The production of pheomelanin appears to be dependent on a loss-of-function mutation in the MC1R transmembrane molecule (melanocyte-stimulating hormone receptor). Therefore, individuals with this mutation produce less melanin and more pheomelanin, making their hair reddish in color. Individuals with this type of mutation have a greater incidence of melanoma.
7. **B.** Histologic features of warts include marked epidermal hyperplasia, eosinophilic cytoplasmic inclusions, and deeply basophilic nuclei. By electron microscopy, many intranuclear viral particles can be observed in the keratinocytes.
8. **B.** Hair follicles are present only in thin skin. They are associated with sebaceous glands and arrector pili smooth muscle bundles.
9. **C.** Eccrine sweat glands are simple, coiled tubular glands that have a duct lined by a stratified cuboidal epithelium. They are found in both thick and thin skin and are classified as merocrine glands, meaning they release only their secretory product, which does not include cells or portions of cells.
10. **A.** The photomicrograph displays both eccrine and apocrine sweat glands. Apocrine sweat glands are limited to the axilla, areola of the breast, the perianal region, and the ceruminous glands of the external ear canal.

chapter 13

Respiratory System

I. OVERVIEW—RESPIRATORY SYSTEM

A. The respiratory system, the lungs and a series of *airways* that connect the lungs to the external environment, can be functionally classified into two major subdivisions: a *conducting portion*, consisting of airways that deliver air to the lungs, and a *respiratory portion*, consisting of structures within the lungs in which oxygen in the inspired air is exchanged for carbon dioxide in the blood.

B. The components of the respiratory system possess characteristic lining epithelia, supporting structures, glands, and other features, which are summarized in Table 13.1 and Figure 13.1.

table 13.1 Comparison of Respiratory System Components

Division	Support	Glands	Epithelium	Ciliated Cells	Goblet Cells	Special Features
Nasal cavity						
Vestibule	Hyaline cartilage	Sebaceous and sweat glands	Stratified squamous keratinized	No	No	Vibrissae
Respiratory	Bone and hyaline cartilage	Seromucous	Pseudostratified ciliated columnar	Yes	Yes	Large venous plexuses
Olfactory	Nasal conchae (bone)	Bowman glands	Pseudostratified ciliated columnar (tall)	Yes	No	Bipolar olfactory cells, sustentacular cells, basal cells, nerve fibers
Nasopharynx	Muscle	Seromucous	Pseudostratified ciliated columnar	Yes	Yes	Pharyngeal tonsil, entrance of Eustachian tube
Larynx	Hyaline, elastic cartilage	Mucous, seromucous	Stratified squamous nonkeratinized, pseudostratified ciliated columnar	Yes	Yes	Vocal cords, striated muscle (vocalis), epiglottis
Trachea **Primary bronchi**	C-shaped hyaline cartilage rings	Mucous, seromucous	Pseudostratified ciliated columnar	Yes	Yes	Trachealis (smooth) muscle, elastic lamina, two mucous cell types, short cells, diffuse endocrine cells
Intrapulmonary bronchi	Plates of hyaline cartilage	Seromucous	Pseudostratified ciliated columnar	Yes	Yes	Two helically oriented ribbons of smooth muscle

(*continued*)

table 13.1 Comparison of Respiratory System Components (*continued*)

Division	Support	Glands	Epithelium	Ciliated Cells	Goblet Cells	Special Features
Primary bronchioles	Smooth muscle	None	Simple ciliated columnar to simple cuboidal	Yes	Only in larger ones	Club cells (formerly Clara cells)
Terminal bronchioles	Smooth muscle	None	Simple cuboidal	Some	None	Club cells (Clara cells)
Respiratory bronchioles	Some smooth muscle	None	Simple cuboidal except where interrupted by alveoli	Some	None	Occasional alveoli, Club cells (Clara cells)
Alveolar ducts	Smooth muscle at alveolar openings, some reticular fibers	None	Simple squamous	None	None	Linear structure formed by adjacent alveoli, types I and II pneumocytes, alveolar macrophages
Alveoli	Reticular fibers, elastic fibers at alveolar openings	None	Simple squamous	None	None	Types I and II pneumocytes, alveolar macrophages

Modified with permission from Gartner LP. *Color Atlas of Histology*. 7th ed. Baltimore, MD: Wolters Kluwer; 2018:324.

II. CONDUCTING PORTION

This portion of the respiratory system includes the nose, nasopharynx, larynx, trachea, bronchi, and bronchioles of decreasing diameters, including and ending at the terminal bronchioles. These structures **warm**, **moisten**, and **filter the air** before it reaches the respiratory components, where exchange of gases occurs (see Table 13.1).

A. The nasal cavity is subdivided by the *median nasal septum* into right and left nasal cavities, each leading to the paranasal sinuses, thus providing a large surface area for filtering, moistening, and warming the inspired air.

1. The **nares** are the nostrils; their outer portions are lined by **thin skin**.
   a. They open into the **vestibule**, the first portion of the nasal cavity, where the epithelial lining becomes **nonkeratinized**. Posteriorly, the lining changes to **respiratory epithelium** (pseudostratified ciliated columnar epithelium with goblet cells).
   b. The vestibule has **vibrissae** (thick, short hairs), which filter large particles from the inspired air and a richly **vascularized** lamina propria (many venous plexuses) and contain **seromucous glands**.
2. Each **nasal cavity** contains bony shelves that originate from the lateral nasal wall and project into the nasal cavity. These are the **superior**, **middle**, and **inferior conchae** (**turbinate bones**). Their structure and placement within the nasal cavity divide it into separate regions, thereby introducing turbulence to the air flow. Because they are covered by respiratory epithelium, their presence increases the surface area for warming, filtering, and moistening the inspired air.

CLINICAL CONSIDERATIONS

Abuse of cocaine by inhalation has long been known to result in the perforation of the nasal septum. More recent reports have shown that individuals who "snort" any of a number of other recreational drugs, such as heroin, benzodiazepines, methamphetamine, and other opioids, for a prolonged period of time also display inflammation and ulceration of the nasal mucosa as well as perforation of the nasal septum. Moreover, a 34-year-old male who abused acetaminophen by inhalation reportedly suffered severe damage to his soft palate, partial destruction of the hard palate, and perforation of his nasal septum.

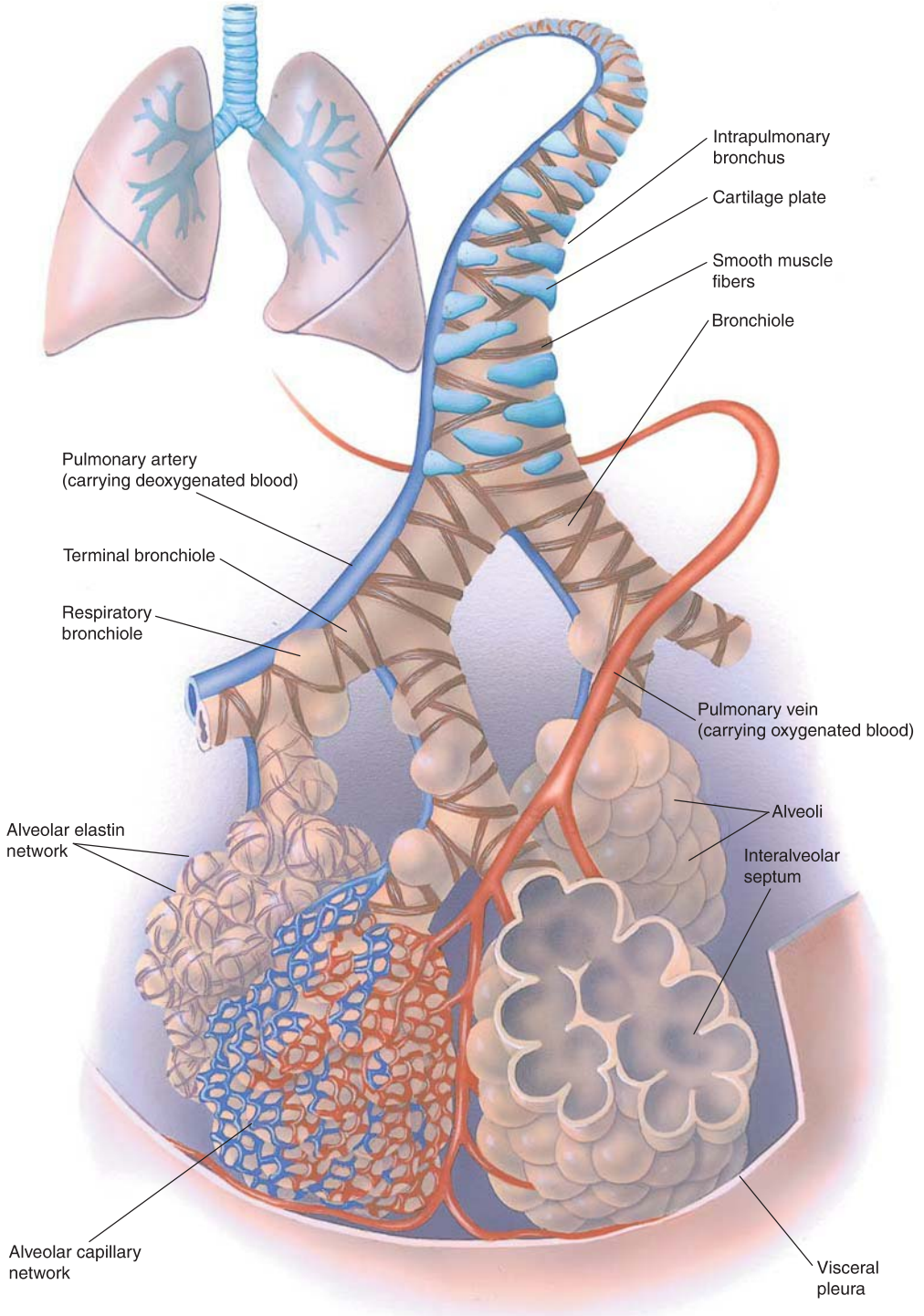


FIGURE 13.1. Conducting and respiratory portions of the respiratory system. (From Gartner LP. *Color Atlas and Text of Histology*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2018:330.)

3. **Paranasal sinuses** are air-filled, hollowed-out portions of the sphenoid, frontal, ethmoid, and maxillary bones. These air sinuses are lined by a thin respiratory epithelium, but the precise function of the paranasal sinuses is not known.
4. The **olfactory epithelium**, located in the roof of the nasal cavity, on either side of the nasal septum and on the superior nasal conchae, is a tall, **pseudostratified columnar epithelium** consisting of olfactory cells, supporting (sustentacular) cells, and basal cells (stem cells). It has a lamina propria that contains many **veins** and **unmyelinated nerves** and houses **Bowman glands**.
   a. **Olfactory cells** are **bipolar nerve cells** characterized by a bulbous apical projection (**olfactory vesicle**) from which several modified cilia, known as olfactory cilia (olfactory hairs), extend.
      (1) **Olfactory cilia** are very **long**, **nonmotile cilia** that extend over the surface of the olfactory epithelium and act as receptors for odor.
      (2) Their proximal third contains a typical **9 + 2 axoneme pattern**, but their distal two-thirds are composed of nine peripheral **singlet** microtubules surrounding a central pair of microtubules.
   b. **Supporting** (**sustentacular**) **cells** possess nuclei that are more apically located than those of the other two cell types. They have many **microvilli** and a prominent **terminal web** of filaments.
   c. **Basal cells** form an incomplete layer of cells that rest on the basal lamina but do not extend to the surface. They are believed to be **regenerative** for all three cell types.
   d. **Bowman glands** (serous glands) lie deep to the epithelium and produce a **thin, watery secretion** that is released onto the olfactory epithelial surface via narrow ducts. Odorous substances (known as **odorants**) dissolved in this watery fluid are detected by the olfactory cilia. The secretion also flushes the epithelial surface, preparing the receptors to receive new odorous stimuli.

B. **The nasopharynx, the posterior continuation of the nasal cavities, becomes continuous with the oropharynx at the level of the soft palate.** It is lined by **respiratory epithelium**, whereas the oropharynx and laryngopharynx are lined by **stratified squamous nonkeratinized epithelium.**
1. The lamina propria of the nasopharynx, located beneath the respiratory epithelium, contains **mucous** and **serous glands** as well as an abundance of lymphoid tissue known as **Waldeyer's ring**, including the **pharyngeal tonsil**. When the pharyngeal tonsil is inflamed, it is called an **adenoid**.
2. Opening into the right and left lateral walls of the nasopharynx are the **auditory tubes** (**Eustachian tubes**), each arising from its respective middle ear cavity.

C. **The larynx connects the pharynx with the trachea.** It functions to produce sounds and close the air passage during swallowing.
1. The wall of the larynx is supported by **hyaline cartilages** (thyroid, cricoid, and lower part of arytenoids) and **elastic cartilages** (epiglottis, corniculate, and tips of arytenoids) and possesses **skeletal muscle**, connective tissue, and **glands**.
2. The **vocal cords** consist of skeletal muscle (the **vocalis muscle**), the **vocal ligament** (formed by a band of elastic fibers), and a covering of **stratified squamous nonkeratinized epithelium**.
   a. Contraction of the laryngeal muscles changes the size of the opening between the vocal cords, which affects the pitch of the sounds caused by air passing through the larynx.
   b. Inferior to the vocal cords, the lining epithelium changes to **respiratory epithelium**, which lines air passages down through the trachea and intrapulmonary bronchi.
3. **Vestibular folds** (**false vocal cords**), lying superior to the vocal cords, are folds of loose connective tissue that contain glands, lymphoid aggregations, and fat cells and are covered by a mixture of **nonstratified and stratified squamous nonkeratinized epithelium**.

D. **The trachea (Fig. 13.2; also see Table 13.1) is the largest conducting section of the respiratory system.** In the adult, it is approximately 11 cm in length with an internal diameter of about 1.5 to 2 cm. The trachea bifurcates into the right and left **extrapulmonary (primary) bronchi**, each of which enters the hilum of the lung on its side. The walls of the trachea, composed of a mucosa, submucosa, and adventitia, are supported by **C-shaped hyaline cartilages** (C-rings), whose open ends face posteriorly. Smooth muscle (**trachealis muscle** in the trachea) extends between the open ends of these cartilages. Dense **fibroelastic** connective tissue is located between adjacent C-rings, permitting elongation of the trachea during inhalation.

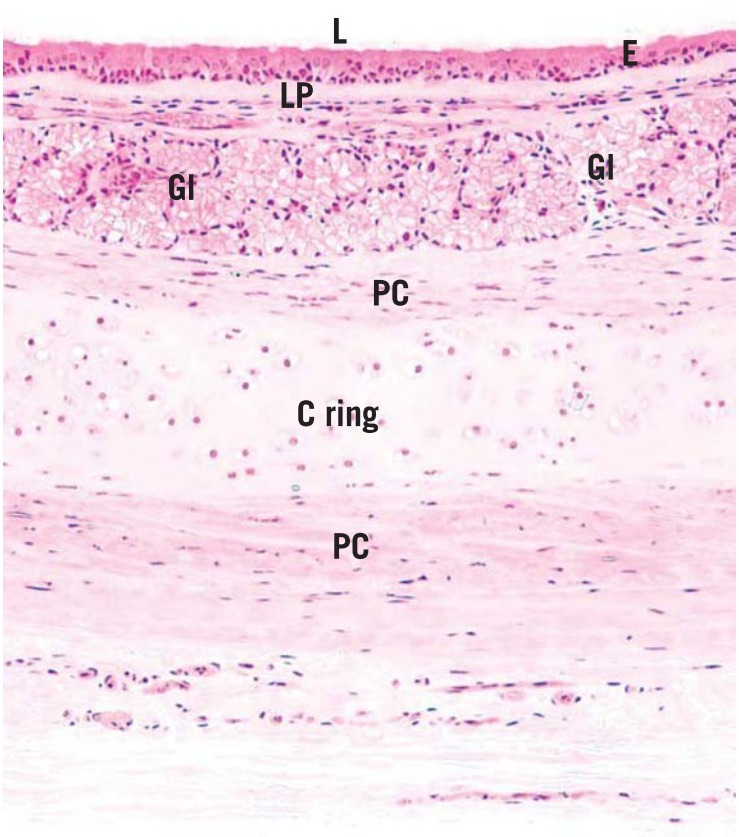


FIGURE 13.2. A light micrograph of the human trachea displays its lumen (L) lined by a pseudostratified ciliated columnar epithelium (E). Deep to the epithelium is the lamina propria (LP) and seromucous glands (GI) in the submucosa. The trachea is supported by C-shaped rings of hyaline cartilage (C-ring), which is surrounded by a perichondrium (PC) (×132).

CLINICAL CONSIDERATIONS

In rare circumstances, congenital enlargement of the trachea and the bronchi occurs, a condition known as **tracheobronchomegaly** (**Mounier–Kuhn syndrome**), a function of an autosomal recessive trait. The tracheal diameter of affected males is greater than 2.5 cm and greater than 2.1 cm in females. The large diameters compromise normal respiration, leading to repeated, long-term respiratory tract infections and the abundant presence of a mixture of mucus and pus. The wide trachea and primary bronchi lead to the widening of smaller airway passages. Controlling infections is essential in individuals with this condition, and long-term antibiotic and inhaled steroid therapy is frequently indicated.

1. **Mucosa** is composed of two layers, the respiratory epithelium and the lamina propria, with an intervening basement membrane.
   a. The **respiratory epithelium** in the trachea possesses five cell types (see Table 13.2).
      (1) **Ciliated cells** have long, actively motile cilia that beat toward the mouth, moving inhaled particulate matter trapped in mucus toward the oropharynx, thus protecting the delicate lung tissue from damage. They also have **microvilli** on their apical surfaces.
      (2) Mature **goblet cells** are goblet shaped and are filled with **large secretory granules**, containing **mucinogen droplets**, which are secreted onto the epithelial surface to trap inhaled particles.
      (3) **Small granule–mucous cells** (**brush cells**) contain varying numbers of **small mucous granules** and display many uniform microvilli on their apical surfaces. They actively **divide** and often replace recently desquamated cells. Some authors believe that they are goblet cells that have secreted their mucinogen.

table 13.2 Cells of the Respiratory Epithelium

Cells	Function	Miscellaneous
Ciliated cells	Move inhaled particulate matter	Motile cilia and microvilli
Goblet cells	Manufacture mucinogen	Goblet shaped with secretory granules
Brush cells	Divide to replace cells	Goblet cells that released mucinogen
DNES cells	Manufacture polypeptide hormones	Also known as small-granule cells
Basal cells	Stem cells	Replace shed cells of the epithelium

DNES, diffuse neuroendocrine system.

(4) **Diffuse neuroendocrine system cells**, also known as **small-granule cells**, contain many small granules concentrated in their **basal** cytoplasm.
  (a) They synthesize different **polypeptide hormones** and **serotonin**, which often exert a local effect on nearby cells and structures (**paracrine regulation**).
  (b) The peptide hormones may also enter the bloodstream and have an **endocrine effect** on distant cells and structures.

(5) **Basal cells** are short cells that rest on the basal lamina but do not extend to the lumen; thus, this epithelium is pseudostratified.
  (a) They are stem cells that are able to **divide** and replace the other cell types.

b. The **basement membrane**, interposed between the epithelium and the lamina propria, is thicker here than in most other places. The **lamina propria** is a thin layer of connective tissue that contains longitudinal **elastic fibers** separating the lamina propria from the submucosa.

2. The **submucosa** is a connective tissue layer containing **seromucous glands**.
3. The **adventitia** contains **C-shaped hyaline cartilages** and forms the outermost layer of the trachea.

E. Extrapulmonary (primary) bronchi **are the continuation of the trachea as it divides into the left and right bronchi.** The left bronchus is approximately 4.1 to 4.7 cm in length and 16 mm in width and diverges from the median plane at an angle of 45°, whereas the right bronchus is 2.5 to 3.4 cm in length and 18 mm in diameter and diverges from the median plane at an angle of 25°. Histologically, the bronchi have the same appearance as the trachea, but they have a narrower diameter. The right bronchus divides into three secondary bronchi to enter the three lobes of the right lung, and the left bronchus divides into two secondary bronchi to enter the two lobes of the left lung.

CLINICAL CONSIDERATIONS

The **right primary bronchus** is shorter, wider, and straighter, coming off the trachea, than the left bronchus; therefore, if a foreign object, such as food, is aspirated, the chances are that it will be lodged in the right primary bronchus rather than in the left primary bronchus.

Both acute tracheitis and **acute bronchitis** (**chest cold**), commonly occurring conditions that last for no longer than 3 weeks, are indicated by constant coughing and mucus production, when the mucosa of the trachea and/or primary bronchi become inflamed because of (mostly) viral assault; therefore, antibiotics should not be prescribed unless the causative agent is known to be bacteria. Because pneumonia, acute tracheitis, and acute bronchitis present with constant coughing, the physician has to eliminate the possibility of pneumonia either by radiographic examination or by clinical observations.

Chronic bronchitis has similar symptoms but of much longer duration (three or more months). The most common form of chronic bronchitis is **chronic obstructive pulmonary disease** (**COPD**) and is the result of long-term inhalation of tobacco smoke, coal dust (in coal miners), textile dust (in textile workers), grain dust (in millers), or working in other dust-laden environments.

F. Intrapulmonary bronchi (secondary bronchi) **(Fig. 13.3; also see Table 13.1) are lined by *respiratory epithelium*; they arise from subdivisions of the primary bronchi as these enter the hilum of the lung. Spiraling smooth muscle bundles** separate the lamina propria from the **seromucous glands** containing submucosa. Instead of C-shaped cartilaginous rings, the adventitia of intrapulmonary bronchi have **plates of irregularly shaped cartilage.** Intrapulmonary bronchi divide many times and give rise to **lobar** and segmental bronchi.

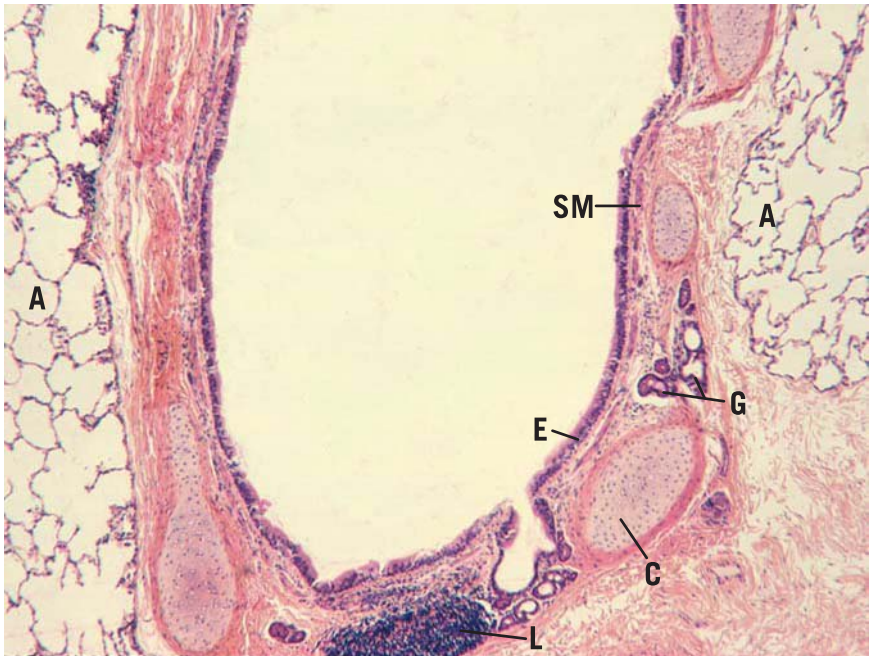


FIGURE 13.3. A light micrograph of an intrapulmonary bronchus cut in cross section. Lining its lumen is a pseudostratified ciliated columnar epithelium with goblet cells (E). Beneath the epithelium in the lamina propria of loose, fibroelastic connective tissue are bundles of smooth muscle (SM) cells wrapped in a spiraling arrangement around the lumen. In the submucosal connective tissue outside of the SM are irregular plates of cartilage (C), seromucous glands (G), and lymphoid tissue (L). Alveoli (A) are evident in the nearby respiratory tissue (×75).

CLINICAL CONSIDERATIONS

Lung cancer is the leading cause of death from cancer in men and women, 90% of which is caused by smoking cigarettes. Two types of lung cancer with increased incidence in smokers include squamous cell carcinoma and small cell (oat cell) carcinoma. Because lung cancer is frequently diagnosed in its later stages, less than 20% of patients diagnosed with lung cancer survive for more than 5 years.

Small cell (oat cell) carcinoma is a highly aggressive carcinoma of bronchial origin whose incidence is greatly increased in smokers. Although it comprises less than 15% of lung cancers, it is very aggressive, grows at a rapid pace, and usually metastasizes far and wide prior to its discovery. It has a poor prognosis.

Non–small cell carcinoma is the most prevalent form, comprising at least 85% of all lung cancers. The three forms of non–small cell cancers of the lung are squamous cell carcinomas, adenocarcinomas, and large cell carcinomas.

Usually, **squamous cell carcinoma** arises in the bronchi, where cigarette smoking causes the respiratory epithelium to change to a stratified squamous epithelium (a metaplastic change). Then, a disorderly proliferation of cells showing great variability in nuclear size and shape occurs in the epithelium (dysplasia), followed by atypical changes that result in a carcinoma (a malignant neoplasm), but it does not usually spread beyond the lungs or its lymph nodes. Approximately 30% of all lung cancers are of the squamous cell type.

Adenocarcinomas account for about 40% of all lung cancers and are more common in women than in men. Most of the cases of adenocarcinoma are smoking related, but it frequently occurs in individuals who are nonsmokers. Of all the lung cancers, this has the best prognosis.

Large cell carcinomas constitute less than 15% of lung cancers. These cancer cells metastasize outside the lung to lymph nodes.

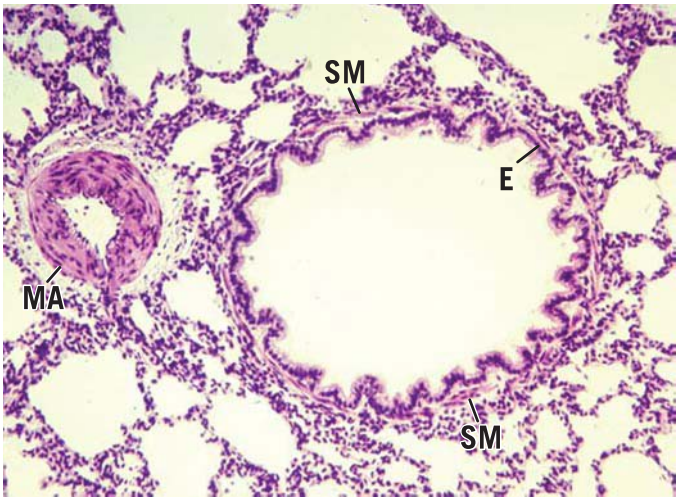


FIGURE 13.4. A light micrograph of a bronchiole in cross section. A simple columnar epithelium (E) lines its lumen, and smooth muscle (SM) cells support its wall. Surrounding the bronchiole is lung tissue with alveoli, and no cartilage or glands are present. Nearby, a muscular artery (MA) is evident (×75).

G. Primary and terminal bronchioles lack glands in their submucosa. Their walls contain **smooth muscle** rather than cartilage plates (Fig. 13.4; also see Table 13.1).

1. **Primary bronchioles** have a diameter of 1 mm or less and are lined by epithelium that varies from **ciliated columnar** with **goblet cells** in the larger airways to **ciliated cuboidal** with **club cells** (formerly known as **Clara cells**) in the smaller passages.
   a. They divide to form several terminal bronchioles after entering the **pulmonary lobules**.
2. **Terminal bronchioles**, the **most distal part of the conducting portion** of the respiratory system, are lined by a **simple cuboidal epithelium** that contains mostly **club cells**, some ciliated cells, and no goblet cells and have a diameter of less than 0.5 mm.
   a. **Club cells** divide, and some of them differentiate to form ciliated and nonciliated cells.
      (1) They **secrete** a **surfactant-like** material that reduces **alveolar surface tension** preventing the collapse of alveoli. They also produce **club cell secretory protein** whose function is assumed to be the protection of the respiratory epithelium.
      (2) They **metabolize airborne toxins**, a process that is carried out by cytochrome P450 enzymes in their abundant smooth endoplasmic reticulum.

CLINICAL CONSIDERATIONS

Asthma is marked by widespread **constriction of smooth muscle in the bronchioles**, causing a decrease in their diameter, and is associated with **extremely difficult expiration** of air, **accumulation of mucus** in the passageways, and **infiltration of inflammatory cells**. It is often treated with drugs, such as albuterol, that act to relax the bronchiolar smooth muscle cells and dilate the passageways and/or treated with corticosteroids, which are anti-inflammatory. Recent studies have demonstrated that **taste receptors** on the smooth muscle cells of bronchioles of the lungs respond to **bitter tastes**, and, when stimulated by a bitter tastant, they cause bronchiolar smooth muscles to relax and the bronchioles to open to 90% of their normal volume. Current work is proceeding to develop aerosolized substances that can be used to stimulate these receptors.

An **acute asthmatic response** has a number of mediators, namely, acetylcholine, histamine, nitric oxide, and leukotrienes. The neurotransmitter **acetylcholine** binds to muscarinic receptors of smooth muscle cells, causing them to contract and reduce the diameter of the airways. **Histamine** released by mast cells binds to histamine receptors of smooth muscle cells, causing them to contract and reduce the diameter of the airways. **Nitric oxide**, formed by inflammatory cells and by the epithelial cells of the bronchiolar epithelium of asthma patients, should act as a bronchodilator. However, in asthma patients, too much nitric oxide produced has a tendency to form peroxynitrite, which damages the airway epithelium, thus exacerbating the asthmatic condition. **Leukotrienes**, formed from arachidonic acid of mast cell membranes, also cause bronchial smooth muscle contraction, reducing the diameter of the airways.

III. RESPIRATORY PORTION (Fig. 13.5)

This portion of the respiratory system includes the respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli, all in the lung. The **exchange of gases** takes place in this portion of the respiratory system.

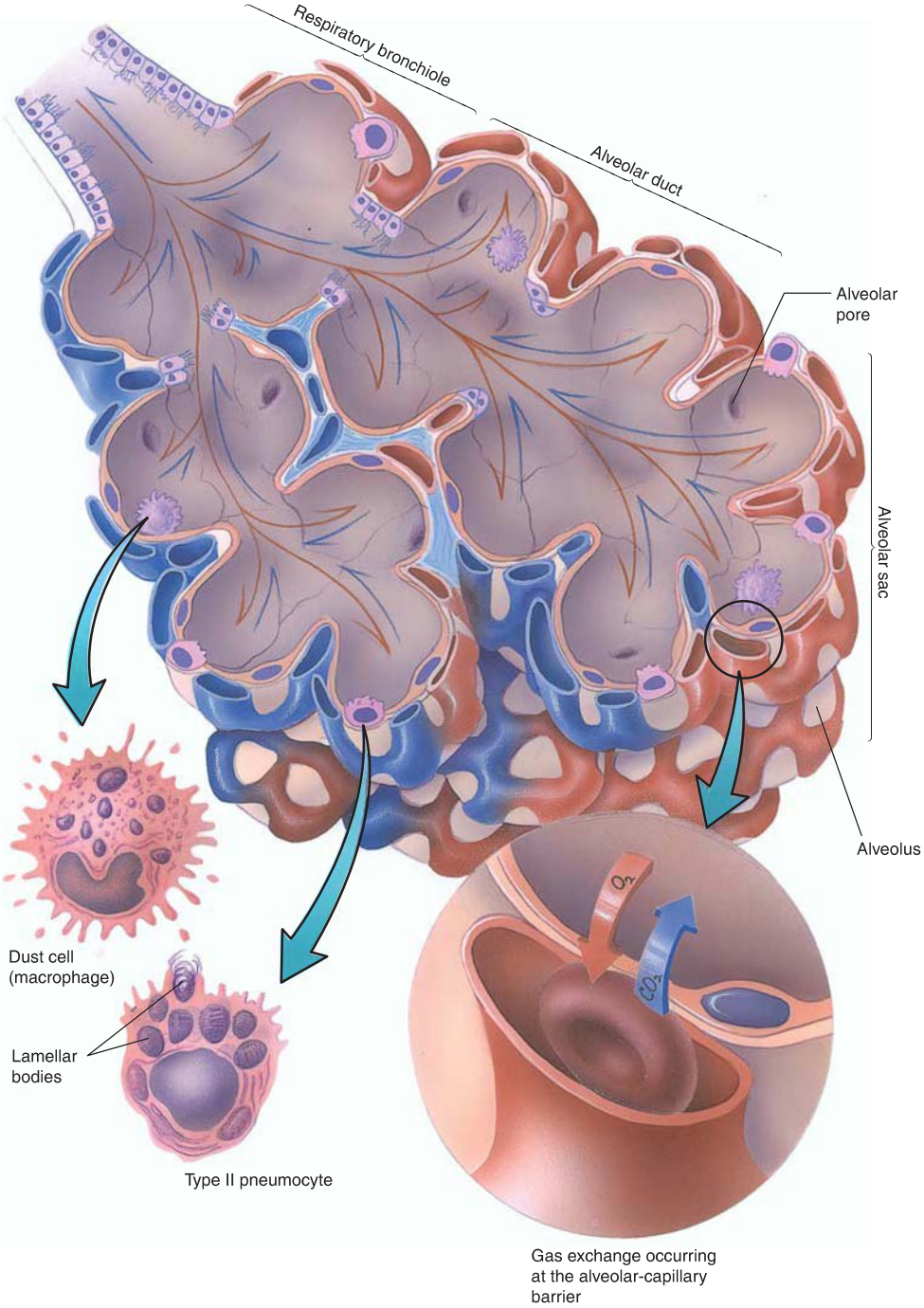


FIGURE 13.5. Components of the respiratory portion of the respiratory system, including a respiratory bronchiole, alveolar duct, and alveolar sac, are illustrated, as well as the exchange of oxygen (O_2) and carbon dioxide (CO_2) across the blood–gas barrier. (From Gartner LP. *Color Atlas of Histology*. 7th ed. Baltimore, MD: Wolters Kluwer; 2018:331.)

A. Respiratory bronchioles (Fig. 13.6; also see Table 13.1) mark the transition from the conducting to the respiratory portion of the respiratory system. They are lined by a **simple cuboidal epithelium** that contains mostly **club cells** and some **ciliated cells**, except where their walls are interrupted by **alveoli**, the sites where exchange of gases occurs and where the lining abruptly changes to a simple epithelium composed of highly attenuated squamous cells.

B. Alveolar ducts (Fig. 13.7; also see Table 13.1) are *linear passageways* continuous with the respiratory bronchioles whose walls consist of *adjacent alveoli*, which are separated from one another only by an *interalveolar septum*.

1. Alveolar ducts, lined by **type II pneumocytes** and the highly **attenuated simple squamous epithelium** of **type I pneumocytes**, are the most distal portion of the respiratory system to contain **smooth muscle cells**, which rim the openings of adjacent alveoli and which often appear as **knobs** in histologic sections.

C. Alveolar sacs are expanded outpouchings of numerous alveoli at the distal ends of alveolar ducts (see Fig. 13.7).

D. Alveoli are pouch-like evaginations about 200 μm in diameter in the walls of respiratory bronchioles, in alveolar ducts, and in alveolar sacs, have thin walls, across which oxygen and carbon dioxide diffuse between the air and the blood. About 500 million alveoli exist in the lung, and their total surface area approximates that of a singles tennis court.

1. **Overview**
   a. **Alveoli** are lined by a **highly attenuated simple squamous epithelium** composed of types I and II **pneumocytes**.
   b. They are separated from each other by **interalveolar septa** that may contain one or more **alveolar pores** (pores of Kohn). These pores permit equalization of pressure between alveoli.
   c. They are rimmed by **elastic fibers** at their openings (except in alveolar ducts, where they are rimmed by smooth muscle cells) and are supported by many **reticular fibers** in their walls.

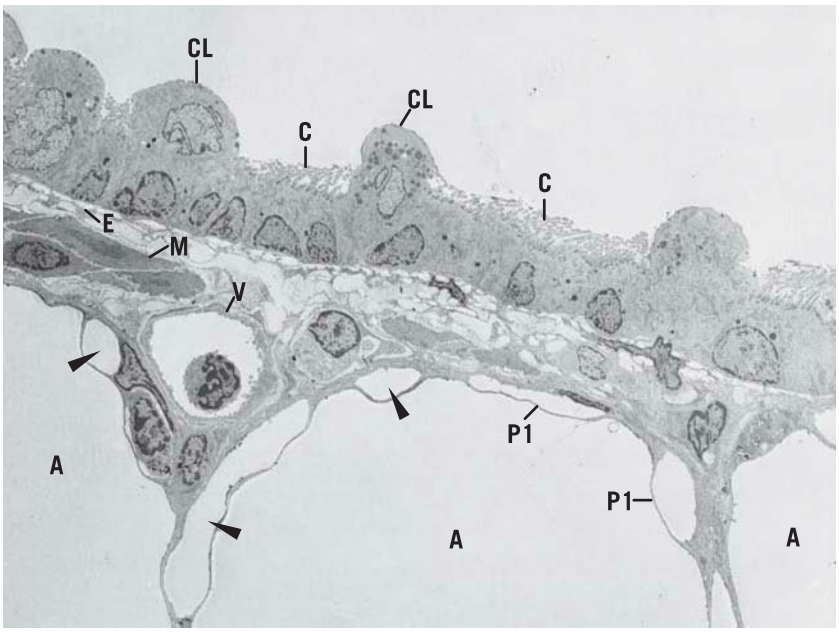


FIGURE 13.6. A low-magnification electron micrograph showing part of a terminal or respiratory bronchiole lined by a simple cuboidal epithelium composed of two cell types: club cells (CL) and ciliated cells (C). In the wall of the bronchiole, smooth muscle cells (M) and elastic tissue (E) are present. A venule (V) containing a white blood cell, several capillaries (*arrowheads*) cleared of blood cells, and alveoli (A) lined by the markedly thin cytoplasm of type I pneumocytes (P1) are also present (×1,500).

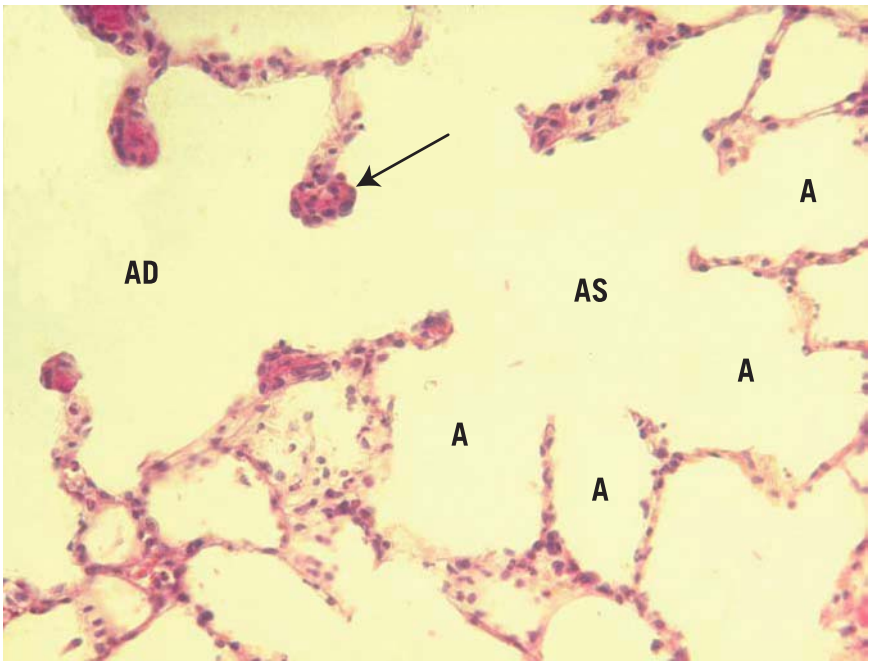


FIGURE 13.7. A light micrograph of an alveolar duct (AD) leading from a respiratory bronchiole into an alveolar sac (AS). The alveolar duct consists of adjacent alveoli, separated from one another only by an interalveolar septum. At the rims of the adjacent alveoli are a few smooth muscle cells (*arrow*) that appear as knobs in histologic sections. Notice that the rims of alveoli (A) in the alveolar sac do not contain smooth muscle.

2. **Alveolar cells**
   a. **Type I pneumocytes** (**type I alveolar cells**) have an extremely **thin cytoplasm** that may be less than 80 nm thick (see Fig. 13.6) and cover about 95% of the alveolar surface; they form part of the blood–gas barrier where exchange of oxygen and carbon dioxide occurs.
      (1) They form **tight junctions** with adjacent cells, may have **phagocytic** capabilities, and are **not** able to divide.
   b. **Type II pneumocytes** (**type II alveolar cells**, **great alveolar cells**, **granular pneumocytes**, **and septal cells**) (Fig. 13.8) are **cuboidal** and are most often found **near septal intersections**. They bulge into the alveolus and have a free surface that contains short **microvilli** around their peripheral borders and form **tight junctions** with adjacent cells.
      (1) These cells not only **divide** and **regenerate** both types of alveolar pneumocytes but also synthesize **pulmonary surfactant**, which is stored in cytoplasmic **lamellar bodies**.
         (a) **Pulmonary** surfactant consists of **phospholipids**, **dipalmitoylphosphatidylcholine**, the four apolipoproteins, **surfactant-associated proteins** (known as **SP-A**, **SP-B**, **SP-C**, **and SP-D**), and **cholesterol**. It forms **tubular myelin** (a network configuration) when it is first released from lamellar bodies; it then spreads to produce a **monomolecular film** over the alveolar surface, forming a **lower aqueous phase** and a **superficial lipid phase**.
         (b) Pulmonary surfactant **reduces the surface tension** at the **air–liquid interface** of the alveolar surface, permitting the alveoli to expand easily during inspiration and preventing alveolar collapse during expiration. Additionally, surfactant reduces fluid accumulation in the alveoli. Moreover, SP-A and SP-D, apolipoproteins of the surfactant, participate in innate immunity by binding to bacterial and viral surfaces, and in that fashion **opsonizing** them. The opsonized microorganisms are recognized and phagocytosed by **macrophages** (**dust cells**) of the lung.

FIGURE 13.8. Electron micrograph of a type II pneumocyte that synthesizes surfactant and stores it in lamellar bodies (LB) in its cytoplasm. Type II pneumocytes are present mainly near the septal intersections and line only small portions of the alveoli (A). They possess microvilli (*arrowhead*) and are cuboidal in shape (×7,000).

CLINICAL CONSIDERATIONS

Neonatal respiratory distress syndrome (**RDS**), previously known as **hyaline membrane disease**, is frequently observed in **premature infants** (<**28 weeks' gestational age**) who **lack adequate amounts of pulmonary surfactant**. It is characterized by **labored breathing**, which results from difficulty expanding the alveoli because of a high alveolar surface tension. If detected before birth or premature labor is suspected, RDS can often be prevented by prolonging pregnancy and sometimes by administering **glucocorticoids** to the expectant mother a few days prior to delivery to help induce the synthesis of surfactant by the baby.

Spontaneous pneumothorax is the collection of gas in the pleural cavity, the potential space between the visceral and parietal pleurae. It causes sudden sharp, severe chest pain on the same side as the affected lung and leads to shortness of breath. The condition occurs most often in young people who have no known underlying pulmonary disease. But computed tomography scans typically reveal **blebs near the lung surface**, **which rupture**, allowing gas to invade the pleural space and causing the lung to collapse (either partially or completely). A minor lung collapse will often resolve on its own, but, when the pneumothorax is larger, a needle or tube is usually inserted between the ribs to remove the gas over a period of a few days, which permits the lung to reinflate.

The **mechanically gated ion channel Piezo2**, located in the plasmalemmae of neurites in the lung, acts as stretch receptors in the lung and protects the lung from becoming overstretched. Mice genetically modified to have no Piezo2 in their neurite plasmalemmae and in the nerve cell bodies in their jugular ganglia lived only a single day after birth because they were unable to send signals to their brainstem; therefore, they were unable to control their breathing. Other mice, whose nodose ganglia were without Piezo2 channels, survived but were unable to control their Hering–Breuer reflex, which prevents the lungs from overinflating. Defects in the gene coding for Piezo2 channels have been noted in humans, but the symptoms were related to problems with proprioception. More recent investigations did detect poor control of the Hering–Breuer reflex in these individuals.

c. **Alveolar macrophages** (**alveolar phagocytes**; **dust cells**) (see Fig. 13.5) are the principal mononuclear **phagocytes** of the alveolar surface. They remove inhaled dust, bacteria, and other particulate matter trapped in the pulmonary surfactant, thus providing a vital line of defense in the lungs. These alveolar macrophages migrate to the bronchioles after filling with debris. From there, they are carried via **ciliary action** to the upper airways, eventually reaching the oropharynx, where they are either swallowed or expectorated; but they may also exit by migrating into the interstitium and leaving via lymphatic vessels.

CLINICAL CONSIDERATIONS

Asbestosis is a pulmonary disease caused by inhaling asbestos fibers (used in insulation materials, tiles, etc.). The fibers deposit in the alveolar ducts and alveoli. The smaller fibers are phagocytosed by macrophages, but the larger ones penetrate the lung interstitium. Activated macrophages release inflammatory mediators, which lead to **interstitial pulmonary fibrosis** in the walls of respiratory bronchioles, alveolar ducts, and alveoli. **Asbestos bodies**, fibers 10 to 50 µm long encrusted with beads of protein, form in the interstitium and alveolar spaces. The asbestos bodies stain strongly for iron because of the hemoglobin protein released from small hemorrhages that accompany the fibrosis.

Emphysema results from **destruction of alveolar walls** and formation of large cyst-like sacs, reducing the surface area available for gas exchange. It is marked by **decreased elasticity** of the lungs, which are unable to recoil adequately during expiration. In time, the lungs expand and enlarge the thoracic cavity (barrel chest). Emphysema is associated with exposure to **cigarette smoke** and **other substances that inhibit α_1-antitrypsin**, a protein that normally protects the lungs from the action of **elastase** produced by alveolar macrophages. However, it can be a hereditary condition resulting from a defective α_1-antitrypsin. In such cases, gene therapy with recombinant α_1-antitrypsin is being used in an effort to correct the problem and it has recently been successful in boosting the availability of this protective protein.

For 7 years, a 61-year-old man was constantly sick with a nonproductive cough that left him breathless. His physicians were unable to diagnose his problem but ascribed it to a strange condition of **hypersensitivity pneumonitis**, even though the patient was never exposed to the known causative factors of that condition, namely, birds, hot tubs, humidifiers, or molds in the carpets and walls of his home. Interestingly, when he took an extended vacation to Australia, his cough and breathlessness were gone. After the patient died, his daily hobby of playing his bagpipes came to light and that he had left them at home when he went to Australia. Examination of the bagpipes indicated the presence of various molds, yeasts, and fungi, which the patient had been inhaling daily while playing his instrument. This was the causative agent of his hypersensitivity pneumonitis.

E. The interalveolar septum, **the wall, or partition, between two adjacent alveoli, is bounded on its outer surfaces by the extremely thin simple squamous epithelium lining the alveoli.** In its wider regions, it contains many **elastic and reticular fibers** and houses **continuous capillaries** in its central (interior) region.

1. The interalveolar septum accommodates the **blood–gas barrier**, which separates the alveolar airspace from the capillary lumen.
   a. **Structure** (Fig. 13.9)
      (1) The thinnest regions of the blood–gas barrier are 0.2 µm or less in thickness and consist of the following layers:
         (a) **Type I pneumocytes and layer of surfactant** lining the alveolar airspace
         (b) ***Fused*** **basal laminae of type I pneumocytes and capillary endothelial cells**
         (c) **Endothelium of the continuous capillaries** within the interalveolar septum
      (2) Thicker regions of the barrier measure as much as 0.5 µm across and have an **interstitial area** interposed between the two ***unfused*** basal laminae.
   b. **Function.** The blood–gas barrier permits the **diffusion of gases** between the alveolar airspace and the blood. **Oxygen** passes from the alveolus into the capillary, and **carbon dioxide** passes from the capillary blood into the alveolus.

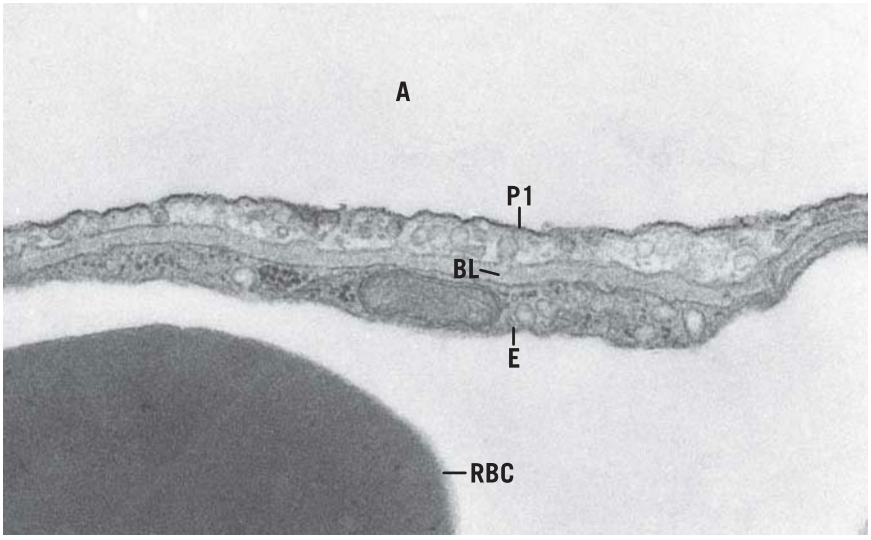


FIGURE 13.9. Electron micrograph showing the blood–gas barrier in the lung, which permits the exchange of gases between the alveolar airspace and the blood. Oxygen diffused from the alveolus (A) into the capillary containing erythrocytes (RBC) and carbon dioxide diffused from the capillary blood into the alveolus. The barrier shown here consists of the following three layers: the cytoplasm of a type I pneumocyte (P1), the fused basal laminae (BL) of a type I pneumocyte and a capillary endothelial cell, and the cytoplasm of the endothelial cell (E) (×14,000).

CLINICAL CONSIDERATIONS

Carbon monoxide poisoning

Carbon monoxide is an odorless, tasteless gas that **binds to hemoglobin** in red blood cells with a **greater affinity than does oxygen**. It is produced whenever fuel-burning appliances are used, which explains the importance of using carbon monoxide detectors. Individuals exposed to carbon monoxide are often unaware of the symptoms it may cause (such as nausea, headache, and sleepiness). Death may occur as the gas replaces oxygen in red blood cells of the lung and blocks the delivery of oxygen to tissues of the body. Treatment consists of exposing the patient to 100% oxygen (sometimes in a hyperbaric chamber) until oxygen displaces the carbon monoxide and recovery occurs.

IV. LUNG LOBULES

Lung lobules vary greatly in size and shape, but each has an apex directed toward the pulmonary hilum and a wider base directed outward. Each lobule contains a **single primary bronchiole**, which enters at the apex and branches to form five to seven terminal bronchioles. The terminal bronchioles in turn divide, ultimately giving rise to alveoli at the base of the lobule.

V. PULMONARY VASCULAR SUPPLY

A. **The pulmonary artery carries blood to the lungs to be *oxygenated*.** It enters the root of each lung and extends branches along the divisions of the bronchial tree. It enters lung lobules, where **its branches follow the bronchioles** (see Fig. 13.4).

B. **In lung lobules, pulmonary veins run in the intersegmental connective tissue, *separated from the arteries*.** After leaving the lobules, the pulmonary veins come close to divisions of the bronchial tree and **run parallel to branches of the pulmonary artery** as they accompany bronchi to the root of the lung.

C. **Bronchial arteries and veins provide nutrients to and remove wastes from the nonrespiratory portions of the lung (bronchi, bronchioles, interstitium, and pleura).** They follow the branching pattern of the bronchial tree and form anastomoses with the pulmonary vessels near capillary beds.

VI. PULMONARY NERVE SUPPLY

The pulmonary nerve supply consists primarily of **autonomic fibers to the smooth muscle of bronchi and bronchioles**. Axons are also present in the thicker parts of the interalveolar septa. **Parasympathetic stimulation** causes **contraction** of pulmonary smooth muscle. **Sympathetic stimulation** causes **relaxation** of pulmonary smooth muscle and can be mimicked by certain drugs that cause dilation of bronchi and bronchioles.

Review Test

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or completions of the statement. Select the ONE lettered answer that is BEST in each case.

1. A patient was examined by the oral surgeon for a lesion on his hard palate and noticed diamond inserts on the labial aspect of the central incisors, signs of oral tobacco use, the presence of a round tongue piercing, and a small fistula that originated in the nasal cavity. When questioned, the patient indicated that the piercing has been in place for almost 10 years but the opening between the oral and nasal cavities occurred only a few weeks ago. What is the most likely cause of the fistula?

(A) The decorative tongue piercing
(B) Intravenous drug abuse
(C) Oral tobacco use
(D) Abuse of drugs by inhalation (snorting)
(E) Diamond implants in the central incisors

2. A patient who has a cough with abundant mucus production for 18 days should be suspected of having which condition?

(A) Pneumonia
(B) Acute tracheitis
(C) Chronic bronchitis
(D) COPD
(E) Small cell carcinoma of the lung

3. A female patient, who never used tobacco products, is diagnosed with lung cancer. What is the most probable type of cancer she has?

(A) Squamous cell carcinoma that originated in the oral cavity
(B) Squamous cell carcinoma that originated in the bronchi
(C) Adenocarcinoma
(D) Large cell carcinoma
(E) Small cell carcinoma

4. Researchers discovered that when patients with asthma inhale odors emanating from substances that have a bitter taste, they can breathe more easily. The reason for this is that taste receptors respond to bitter tastants on smooth muscle cells of which structure?

(A) Trachea
(B) Primary bronchi
(C) Secondary bronchi
(D) Bronchioles
(E) Pulmonary arterioles

5. Which mediator is involved in a patient with an acute asthmatic response?

(A) Acetylcholine
(B) Dopamine
(C) γ-Aminobutyric acid
(D) Serotonin
(E) Glycine

Questions 6, 7, and 8 refer to the following clinical scenario.

A baby born after only 26 weeks of gestation presents with labored breathing in the delivery room. The mother did not receive prenatal care.

6. What is the most probable condition that the newborn is experiencing?

(A) RDS
(B) Pneumothorax
(C) Emphysema
(D) Pneumonia
(E) Inhalation of amniotic fluid

7. What is the underlying cause of the labored breathing?

(A) Lack of complete development of bronchiolar smooth muscle
(B) Lack of complete development of innervation to the respiratory system
(C) Lack of pulmonary surfactant
(D) Lack of ion channel Piezo2
(E) Lack of completely developed Hering–Breuer reflex

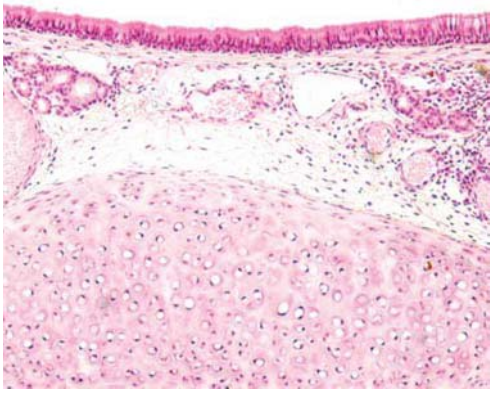
8. Had the mother received proper prenatal care, what would have been the appropriate preventive treatment?

(A) Amniocentesis
(B) Oxygen treatment
(C) Maternal surfactant inhalation
(D) In utero fetal surfactant inhalation
(E) Maternal glucocorticoid administration

9. Which condition is associated with a barrel chest?

(A) Asbestosis
(B) Asthma
(C) Carbon monoxide poisoning
(D) Emphysema
(E) Neonatal RDS

Question 10 is based on the following photomicrograph.



10. The diameter of the structure in the photomicrograph taken from a dead male is 3.1 cm. What is the name of the autosomal recessive trait that this person evidenced?

(A) Spontaneous pneumothorax
(B) Asbestosis
(C) Emphysema
(D) Mounier–Kuhn syndrome
(E) Hypersensitive pneumonitis

Answers and Explanations

1. **D.** The sudden appearance of a fistula between the nasal and oral cavities through the hard palate is a good indication of recreational inhalation (snorting) of drugs by the patient.
2. **B.** The short duration of the symptoms is indicative of an acute rather than a chronic condition. Therefore, the patient probably has chronic tracheitis.
3. **C.** The most common form of lung cancers in patients who never used tobacco products is adenocarcinoma. It is more common in females than in males.
4. **D.** Recent studies have demonstrated that taste receptors on the smooth muscle cells of bronchioles of the lungs respond to bitter tastes, and, when stimulated by a bitter tastant, they cause bronchiolar smooth muscles to relax and the bronchioles to open to 90% of their normal volume.
5. **A.** An acute asthmatic response has a number of mediators, namely, acetylcholine, histamine, nitric oxide, and leukotrienes.
6. **A.** Neonatal RDS (hyaline disease) is frequently observed in premature infants (<28 weeks' gestational age).
7. **C.** Neonatal RDS (hyaline disease) is frequently observed in premature infants (<28 weeks' gestational age) who lack adequate amounts of pulmonary surfactant.
8. **E.** If detected before birth or premature labor is suspected, neonatal RDS can often be prevented by prolonging pregnancy and sometimes by administering glucocorticoids to the expectant mother a few days prior to delivery to help induce the synthesis of surfactant by the baby.
9. **D.** A loss of lung elasticity in emphysema makes it difficult for the lungs to recoil normally during expiration. The lungs and thoracic cavity enlarge, producing a barrel chest.
10. **D.** In rare circumstances, congenital enlargement of the trachea and the bronchi occurs, a condition known as tracheobronchomegaly (Mounier–Kuhn syndrome), a function of an autosomal recessive trait. The tracheal diameter of affected males is greater than 2.5 cm and greater than 2.1 cm in females.

chapter 14

Digestive System: Oral Cavity and Alimentary Tract

I. OVERVIEW—DIGESTIVE SYSTEM

The digestive system is composed of the **oral region**, **alimentary canal** (**esophagus**, **stomach**, and **small** and **large intestines**), and several **extrinsic glands**. It is a hollow tube (highly modified in the oral cavity) of varying diameters whose concentric layers include the **mucosa**, **submucosa**, **muscularis externa**, and **serosa** (or **adventitia**). The digestive system secretes **enzymes** and **hormones** that function in ingestion, digestion, and absorption of nutrients and in the elimination of indigestible materials.

II. ORAL REGION

The oral region is composed of the lips, palate, teeth and associated structures, tongue, major salivary glands, and lingual, palatine, tubal, and pharyngeal tonsils, where the tonsils (collections of lymphoid nodules) form Waldeyer's tonsillar ring, to protect the entryways into the alimentary canal and the respiratory system. The oral region is lined in most places by a **stratified squamous epithelium** whose **epithelial ridges** interdigitate with tall **connective tissue papillae** (connective tissue ridges) of the subjacent connective tissue. The epithelial ridges and the connective tissue ridges are known collectively as the **rete apparatus**. The epithelium and connective tissue together form the mucosa. The oral cavity has three types of mucosae: **lining mucosa**, whose epithelium is nonkeratinized; **masticatory mucosa**, whose epithelium is keratinized (or parakeratinized); and **specialized mucosa**, whose nonkeratinized stratified squamous epithelium is enriched with taste buds. The dorsal surface of the tongue, hard palate, and gingivae are the only regions that possess masticatory mucosa; the dorsum of the tongue, soft palate, and regions of the pharynx possess specialized mucosa; the remainder of the oral cavity is lined by lining mucosa. The histology of the tongue is described at the end of Section II of this chapter.

A. The lips are divided into the *external* (*skin*) *region*, the *vermilion zone*, and the *internal* (*mucosal*) *region*. The first two regions are covered by stratified squamous keratinized epithelium, whereas the internal region is lined by a wet stratified squamous nonkeratinized epithelium.

1. A dense irregular collagenous connective tissue core envelops skeletal muscle.
2. **Sebaceous glands**, **sweat glands**, and **hair follicles** are present in the external region; **minor salivary glands** in the internal region; and occasional, nonfunctional sebaceous glands (known as **Fordyce's granules**) in the internal region and vermilion zone.

B. The palate separates the nasal cavity from the oral cavity and is divided into an anterior *hard palate* (possessing a bony shelf in its core); a posterior *soft palate* (possessing skeletal muscle in its core); and the posterior terminus of the soft palate, the *uvula*. The palate has a nasal aspect and an oral aspect. The entire **nasal aspect** of the palate (with the exception of the uvula) is lined by **pseudostratified ciliated columnar epithelium** (respiratory epithelium).

1. The **hard palate** is lined on its oral aspect by stratified squamous **parakeratinized** to stratified squamous **keratinized** epithelium. It contains adipose tissue anteriorly and minor mucous salivary glands posteriorly in the oral aspect of its connective tissue, also known as the **mucoperiosteum**. The hard palate has a bony shelf in its core.
2. The **soft palate** is lined on its oral aspect by stratified squamous **nonkeratinized** epithelium. It contains minor mucous salivary glands in the oral aspect of its connective tissue.

CLINICAL CONSIDERATIONS

Herpetic stomatitis is caused by herpes simplex virus (HSV) type 1. In the dormant state, this virus resides in the trigeminal ganglia. HSV type 1 infection is very common and is transmitted by kissing. This infection is characterized by painful fever blisters on the lips or in the vicinity of the nostrils. These blisters exude a clear fluid or are covered by a scab.

Angular cheilitis (**perlèche**) is a painful condition, usually in patients older than 50 years of age, in which the corners of the mouth have short erythematous fissures and cracks that are inflamed and may become infected with *Candida albicans* or with occasional secondary bacterial colonization by *Staphylococcus aureus.* Licking the corner of the mouth exacerbates and prolongs the condition. Treatment is usually with an antifungal ointment and, in the case of a secondary bacterial infection, an antibiotic regimen and behavioral modification (i.e., instructing the patient to resist the urge to lick the corners of the mouth).

Cancers of the oral region most commonly affect the lips, tongue, and floor of the mouth. These cancers initially resemble leukoplakia and are asymptomatic. Survival rate is high if these cancers are recognized and treated in their early stages. The vast majority of the cancers of the oral region arise from the various types of stratified squamous epithelium of its lining/covering and belong to the group of cancers known as **squamous cell carcinomas**. Most of these, such as cancers of the lip, palate, tongue, and oral mucosa, are due to tobacco use.

Burning mouth syndrome (**BMS**) is a painful condition in which the patient has a burning sensation of the mouth and/or tongue. In some individuals, the sensation is more of numbness than of burning. Frequently, the condition is accompanied by an altered taste sensation, such as a metallic taste or a bitter taste of inexplicable origin. In some patients, dryness in the mouth due to lessened saliva production is also present. The cause of BMS is not known, although some researchers suggest that the patient is suffering from vitamin B_{12} deficiency, candidiasis, acid influx, certain prescription medications, allergies, the use of dentures, and even depression and anxiety. The condition is more common in women than in men. BMS is categorized into three types, depending on the timing of the presence of symptoms. **Type 1** presents with no symptoms at awakening, and the pain increases as the day progresses; in **type 2**, the burning sensation is present as the patient wakes up and continues as the day progresses; and in **type 3**, the symptoms appear in a random fashion.

C. Teeth **are composed of an internal soft tissue, the *pulp*, and three calcified tissues: *enamel* and *cementum*, which form the surface layer, and *dentin*, which lies between the surface layer and pulp.** As in bone, **calcium hydroxyapatite** is the mineral material in the calcified dental tissues. Teeth have an enamel-covered **crown**, a cementum-covered root, and a **cervix**, the region where the two surface materials meet.

1. **Tooth components**
   a. **Enamel** has a highly calcified matrix with an organic component that is composed mostly of the fibrous keratin-like protein, **enamelin**, a substance that is elaborated by **ameloblasts** during formation of the crown and becomes calcified by the deposition of **calcium hydroxyapatite crystals**. It consists of only 4% organic material and 96% inorganic material and, thus, is the most calcified tissue in the body. Enamel is **acellular after tooth eruption** and therefore cannot repair itself.

CLINICAL CONSIDERATIONS

The bacterial flora of the oral cavity acts on food remnants lodged between teeth and in the gingival sulcus, the normally tiny crevice between the gum and the enamel of the tooth. As the bacteria metabolize the sugars in the food debris, they produce organic acids that can dissolve enough of the calcium-hydroxyapatite crystals to form carious lesions (tooth decay), unless the individual practices good oral hygiene. The use of fluoride in the water supply to increase the fluoride concentration to 0.7 to 1.2 ppm (systemic application), as well as the addition of fluoride in toothpaste (topical application), makes enamel more resistant to bacterial acids by altering the hydroxyapatite crystals to fluoroapatite crystals (fluoride replaces hydroxyl molecules), making it less soluble by the acidic environment. Moreover, the presence of fluoride on the enamel surface catalyzes its remineralization and may decrease the ability of the resident bacteria to form organic acids.

b. **Dentin** surrounds the central **pulp chamber** of the crown and **pulp** (**root**) **canal**. It is manufactured by **odontoblasts**, which persist and continue to elaborate dentin for the life of the tooth; the calcified matrix contains **type I collagen fibers**.
c. **Cementum** has a **type I collagen–containing** calcified matrix, which is produced by cells known as cementoblasts that continue to elaborate cementum even after tooth eruption, as it compensates for the decrease in tooth length resulting from abrasion of the enamel.
d. **Dental pulp** is a gelatinous, richly vascularized connective tissue containing a single layer of **odontoblasts** in its peripheral layer (closest to the dentin). The pulp is richly endowed with fibroblasts and mesenchymal cells, and its connective tissue matrix has thin types I and III collagen fibers. The pulp also has **afferent nerve fibers**. All sensations from the pulp are interpreted as pain in the central nervous system.

2. **Crown formation**
a. The crown begins to form 6 to 7 weeks after conception as a horseshoe-shaped band, the **dental lamina**, which is derived from the **oral epithelium**. A dental lamina develops in each jaw and projects into the underlying **ectomesenchyme**. The development of teeth, known as **tooth germs**, depends on **epithelial–mesenchymal interaction** between the epithelium and the ectomesenchyme (neural crest–derived mesenchymal tissue). This interaction is dependent on various signaling molecules produced by both the epithelium and the ectomesenchyme.
b. A **tooth germ** has two components, the epithelially derived **enamel organ** and the ectomesenchymally derived **dental papilla** surrounded by the ectomesenchymally derived **dental sac**. The enamel organ is responsible for the formation of the **enamel** and **junctional epithelium**, the dental papilla will give rise to **dentin** and the **pulp**, and the dental sac will form the **attachment apparatus**, namely **cementum**, **periodontal ligament**, **bony alveolus**, and the connective tissue of the **gingiva**.
c. The oral ectoderm releases the following factors and gene products: **fibroblast growth factor 8**, **Wnt**, **sonic hedgehog**, **and transforming growth factor-β**.
d. The ectomesenchyme releases **activin βA** and **bone morphogenetic protein 4** (**BMP-4**) as well as the gene products **MSX-1** and **MSX-2** or **DLX-1** and **DLX-2** for proper tooth development.
e. The sequential stages of crown formation of the tooth germ are **bud**, **cap**, **bell**, and **appositional stages**. Ten buds are formed on the maxillary arch and 10 buds are formed on the mandibular arch. The entire crown of each tooth forms **before** the root formation begins.
f. Each bud, in turn, goes through the stages of tooth development on its own pace and, during the **cap stage** of development, forms a **primary enamel knot** (**PEK**) within its enamel organ. The PEK is responsible for the determination of incisor and canine or premolar and molar formation by that particular tooth germ. The PEK forms and releases a number of factors, including BMPs-2 and -4; fibroblast growth factor-4, and gene products Wnt and sonic hedgehog. In order to form teeth with cusps (premolars and molars), the cells of the PEK have to survive; for that, they require epidermal growth factor and fibroblast growth factor-4. In the absence of these two factors, the cells of the PEK undergo apoptosis and the tooth germ will develop into an incisiform tooth (without cusps). If these two factors are present, then the tooth germ will develop into a molariform tooth (with cusps) and a **secondary enamel knot** (**SEK**) will form over each cusp to direct the development of that particular cusp.

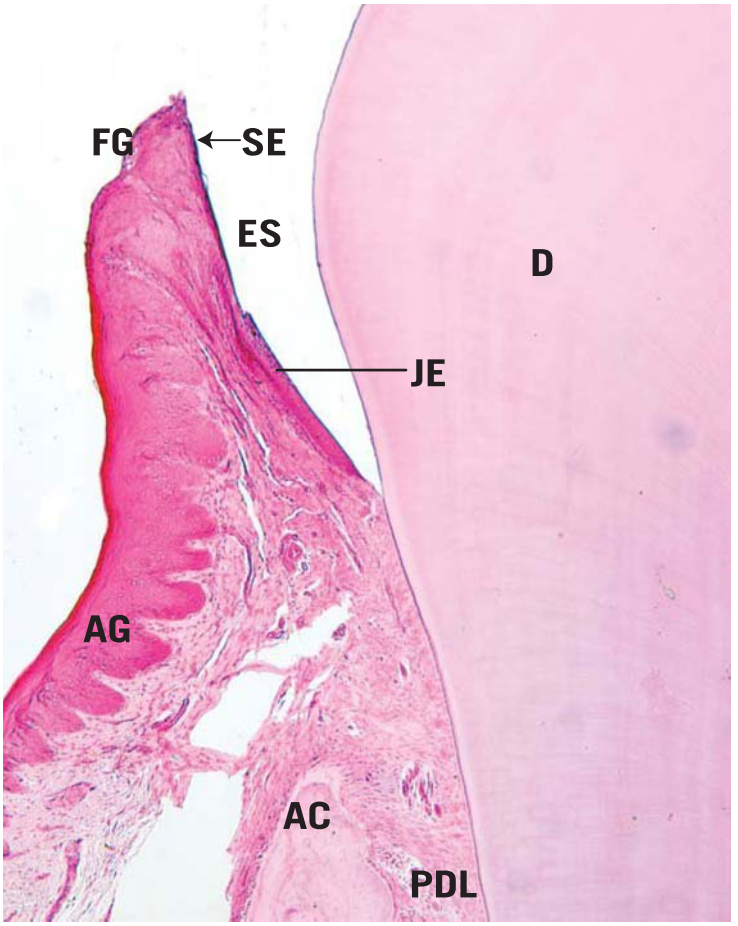


FIGURE 14.1. This low-power photomicrograph of a portion of the tooth and its soft tissue coverings display the dentin (D), the space where the enamel (ES) was before the tissue was decalcified, the free gingiva (FG) and its sulcular epithelium (SE), the attached gingiva (AG) and its junctional epithelium (JE), as well as the coronal portion of the periodontal ligament (PDL) and the crest of the alveolar bone (AC) (×56).

g. During the cap stage of tooth development, another epithelial downgrowth develops, the **succedaneous lamina**, which is responsible for the formation of the **succedaneous tooth** (**permanent tooth**) that will eventually replace the **primary tooth** (**deciduous tooth**) formed by the tooth germ of its origin.

3. **Root formation** follows completion of the crown and is accompanied by tooth eruption.

D. Dental-supporting structures (Fig. 14.1)

1. The **periodontal ligament** is composed of a dense irregular collagenous connective tissue whose type I collagen fibers are arranged in five **principal fiber bundles**, which extend from the cementum to bone (alveolar crest, horizontal, oblique, apical, and interradicular fiber groups), suspending the tooth in its **alveolus**.
2. **Gingivae** (**gums**) are covered by stratified squamous **keratinized** (or **parakeratinized**) epithelium; their collagen fibers are also arranged in five **principal fiber bundles** (alveologingival, dentogingival, circular, dentoperiosteal, and transseptal fiber groups). The epithelium of the gingivae is reflected onto the enamel surface, forming a shallow groove, the **gingival sulcus** that surrounds the neck of the tooth. The epithelium at the base of the sulcus is continuous with a narrow band of epithelial cells, the **junctional epithelium**, which acts as a barrier between the oral cavity and the connective tissue elements of the gingiva.

3. **Alveolar bone** consists of an inner layer of compact bone (**cribriform plate**, or **alveolar bone proper**). There is also an outer layer (**cortical plate**) of compact bone with an intervening layer of cancellous bone (**spongiosa**).

CLINICAL CONSIDERATIONS

Individuals with poor oral hygiene—that is, people who do not brush and/or do not floss their teeth—accumulate a **biofilm** known as **plaque** over their teeth as well as within the gingival sulcus. This plaque is composed of a thin layer of bacteria bound to each other by sugar molecules, which form a source of nutrients for the bacteria. Brushing and flossing remove the plaque. However, if these are not removed, the plaque calcifies within 24 hours, forming a hardened substance, known as **calculus**, which firmly adheres to the tooth surface and grows in size. The calculus acts as a protective cover for the bacteria, which now live and prosper in this anaerobic environment. As the bacterial colony and the calculus increase in size, they damage the gingival epithelium as well as the junctional epithelium, resulting in an inflammatory response from the gingival connective tissue. This protective response is known as **gingivitis**. If gingivitis is permitted to progress, the bacterial invasion will attack the periodontal ligament and the bony alveolus, eliciting a protective response from the periodontal ligament, a process known as **periodontitis**. If this condition is not corrected, it leads to the destruction of the periodontium, the loosening of the tooth in its alveolus, and an eventual loss of the tooth/teeth involved. An estimated 65 million American adults have gingivitis and periodontitis. The most common symptoms of periodontitis are red, swollen gums that receded from the cementoenamel junction and bleed while brushing; deep gingival sulcus; mobile teeth; the presence of pus when gums are squeezed against the teeth; and long-term bad breath.

Researchers have suggested that a strong connection exists between **periodontal disease and heart disease**, but this theory is not universally accepted. Much of the evidence is based on the fact that microbes, especially *Streptococcus sanguis*, spread from the inflamed periodontal tissues to the heart. Patients with no periodontitis present with much fewer *S. sanguis* in the heart. Although this is interesting evidence, individuals with periodontitis and heart disease have many other factors in common, such as unhealthy behaviors including smoking, lack of exercise, and poor diet and conditions like diabetes, obesity, and metabolic disease.

E. Tongue

1. **Overview**
   - **a.** The tongue is divided into an anterior two-thirds and a posterior one-third by the V-shaped **sulcus terminalis**, with its posteriorly pointing apex ending in the **foramen cecum**.
   - **b.** Its dorsal surface is covered by stratified squamous **parakeratinized** to **keratinized epithelium**, whereas its ventral surface is covered by stratified squamous **nonkeratinized epithelium** (Table 14.1). Underlying both epithelial surfaces is a **lamina propria** and **submucosa** of dense irregular collagenous connective tissue; a **core** of skeletal muscle forms the bulk of the tongue.
2. **Lingual papillae** are located on the **dorsal surface of the anterior two-thirds** of the tongue.
   - **a. Filiform papillae** are short, narrow, **highly keratinized** structures lacking taste buds.
   - **b. Fungiform papillae** are mushroom-shaped structures interspersed among the filiform papillae; they contain occasional **taste buds** on their superior aspect.
   - **c. Foliate papillae** are shallow longitudinal furrows on the lateral aspect of the posterior region of the anterior two-thirds of the tongue. Their taste buds degenerate shortly after the second year of life.
   - **d. Circumvallate papillae** are 10 to 15 large circular papillae, each of which is surrounded by a moat-like furrow. They lie just anterior to the **sulcus terminalis** and possess taste buds.
     - **(1) Taste buds**
       - **(a)** Each of the 2,000 to 8,000 taste buds located on the tongue is composed of 60 to 80 spindle-shaped cells that form a barrel-shaped **intraepithelial structure**. These structures are located on the superior surface of fungiform papillae, on the **lateral surfaces**

table 14.1 Summary of the Histologic Features of the Oral Mucosa

Mucosal Region	Type of Epithelium/Mucosa	Height of CT Papilla	Special Comments
Lip			
Skin aspect	Stratified squamous keratin	Medium	Hair, sebaceous and sweat glands
Vermilion zone	Stratified squamous keratin	High	Few sebaceous glands(?)
Mucosal aspect	Stratified squamous nonkeratinized	Medium	Mucous (mixed) minor salivary glands and Fordyce granules
Cheek			
Skin aspect	Stratified squamous keratinized	Medium	Hair, sebaceous and sweat glands
Mucosal aspect	Stratified squamous nonkeratinized	Medium	Mucous (mixed?) minor salivary glands and Fordyce granules
Gingiva			
Free and attached	Masticatory mucosa	High	Tightly bound to the periosteum
Sulcular	Lining mucosa	Low	Lines the gingival sulcus
Junctional epithelium	Stratified squamous nonkeratinized	None	Attached to tooth surface and to gingival connective tissue by hemidesmosomes
Alveolar mucosa	Lining mucosa	Low	Some minor mucous salivary glands
Hard palate*			
Anterior lateral	Masticatory mucosa	High	Adipose tissue in the connective tissue
Posterior lateral	Masticatory mucosa	High	Minor mucous salivary glands in CT
Raphe	Masticatory mucosa	High	Tightly bound to periosteum
Soft palate*	Lining mucosa	Low	Elastic lamina; minor mucous salivary glands
Uvula	Lining mucosa	Low	Minor mucous salivary glands in CT
Floor of the mouth	Lining mucosa	Low	Minor mucous salivary glands in CT
Tongue			
Dorsal surface	Specialized mucosa embedded in masticatory mucosa	Low High	Taste buds; lingual papillae; serous, mucous, and mixed minor salivary glands
Ventral surface	Lining mucosa	Low	Sublingual folds

CT, connective tissue. Hard palate has a bony shelf and soft palate has skeletal muscle in its core.
*The description in this table for the hard palate and soft palate is only for the oral aspect. The nasal aspect of both hard and soft palates is covered by a respiratory epithelium. However, the nasal aspect of the uvula is covered by a stratified squamous nonkeratinized epithelium.

of circumvallate papillae, and in the **walls** of the surrounding moat-like furrows. Each taste bud has a small opening, the **taste pore**, from which microvilli (**taste hairs**) project into the oral cavity (or into the moat surrounding the circumvallate papilla).

(b) Taste buds perceive **salt**, **sour**, **bitter**, **sweet**, and **umami** (glutamate receptor that senses delicious flavors) taste sensations, and some, in individuals who have the genetic capability, may specialize in tasting **fats**. The chemical moieties of the food substances that are recognized by taste buds are known as **tastants**.

(c) Four different cells are recognized by studying electron micrographs of taste buds, three of which are spindle shaped: dark cells (type I cells), light cells (type II cells), and intermediate cells (type III cells) have short life spans; the fourth type are the short, regenerative, basal cells. Type I, II, and III cells form **synapses** with **afferent nerve fibers** that deliver the taste information to the central nervous system.

(d) When basal cells divide, they give rise to a basal cell and a dark cell. As the dark cell matures, it becomes a light cell, and, as it degenerates, it becomes an intermediate cell. These three cell types are **neuroepithelial** cells whose microvilli, the taste hairs, recognize one specific tastant. The process of going from a newly formed dark cell to a dying intermediate cell takes about 10 days. A particular taste bud contains a variety of neuroepithelial cells that recognize all tastants, but each taste bud appears to be specialized to respond to only one or two of the tastants.

(e) Salt and sour tastants stimulate **sodium** and **hydrogen ion channels**, respectively; sweet, bitter, and umami tastants stimulate **G protein–linked receptors**; and fatty tastants stimulate fatty acid transporters.

(f) With light microscopy, only three types of cells were recognized: spindle-shaped neuroepithelial cells, broader-shaped supporting sustentacular cells, and short basal cells. Although still described as such, the electron microscopic interpretations are universally accepted and have supplanted the light microscopic interpretation.

CLINICAL CONSIDERATIONS

A large number of genes code for various G protein–linked receptors located in the membranes of the taste hairs (microvilli): T1R1, T1R2, T1R3, and 1 of 43 different types of T2R (the most common is T2R38). A combination of two of the T1Rs codes for sweet (T1R2 and T1R3) and umami (T1R1 and T1R3) receptors, whereas all T2Rs code for bitter receptors (as with sweet and umami receptors, a combination of two T2R gene codes are required). Individuals who are able to taste fats possess a fatty acid transporter, a cluster of differentiation molecule (CD36) on the membranes of their microvilli. An additional molecule is necessary for sour tastes to be recognized. Alongside the hydrogen ion channel is the product of the polycystic kidney disease 2–like 1 protein gene (PKD2L1 gene), which, in some unknown fashion, interacts with the hydrogen ion channel to recognize the sour taste sensation.

Apparently, the more molecules of a particular tastant that bind to a neuroepithelial cell, the stronger the taste sensation. Taste receptors have also been shown to have binding sites for nontastant molecules that act as **enhancer molecules**. Therefore, when enhancer molecules bind along with tastants, the tastants are locked in the receptor for a longer period of time. Thus, the tastant–enhancer molecule combination augments the taste sensation so that the binding of only a few tastant molecules is interpreted as if many such tastant molecules were present.

The sense of taste is a complex interaction between the information that the brain receives from the taste buds; from sensory cells that determine the temperature, spiciness, and texture of the food; and from **retronasal olfaction**. The process of retronasal olfaction depends on olfactory cells located in the posterior aspect of the nasal cavity, and the odor that they perceive arises from the back of the mouth rather than the more commonly thought of **orthonasal olfaction**, where the odor is perceived via air entering the nasal cavity. An additional component of the perception of taste is the visual information that the brain gleans via the sense of sight. An unusually colored version of a particular food morsel may elicit a sense of disgust, a perceived altered taste, and the inability to consume the food substance.

Recent investigations have demonstrated that a number of organs, other than the tongue and oral cavity, possess taste receptors. These include the brain, nasal cavity and sinuses, trachea and bronchi, lungs, thymus, heart, bone, mammary glands, alimentary canal, pancreas, bladder and urethra, adipose tissue, and testes. Some investigators believe that these receptors interact with the immune system. Two types of defense mechanisms are known to use bitter taste receptors, one is located in the nasal cavity and others are localized in various regions of the body.

The one in the nasal cavity, located on the cilia of epithelial lining cells, binds acyl homoserine lactones released by infectious gram-negative bacteria. In response to the binding, the epithelial cells release nitric oxide, a gas that has bactericidal properties.

The second mechanism relies on both bitter and sweet taste receptors located on cilia of cells known as **solitary chemosensory cells**. As infectious bacteria consume sugars, they release chemicals that bind to bitter receptors that activate the chemosensory cells to release calcium, which diffuses to cells in the vicinity and activates them to release the bactericidal agent defensins. As bacteria are destroyed, the amount of sugars in the region are increased, and they bind to and activate sweet receptors located on the chemosensory cells, thus inhibiting the release of calcium and shutting down the production of defensins by the releasing cells.

(2) Glands of von Ebner are minor salivary glands that deliver their **serous secretion** into the furrow surrounding each papilla, assisting the taste buds in perceiving stimuli. These glands also deliver their saliva into the furrows of the foliate papillae.

3. The **muscular core of the tongue** is composed of bundles of **skeletal muscle fibers** arranged in three planes with **minor salivary glands** interspersed among them.
4. **A lingual tonsil** is located on the dorsal surface of the **posterior one-third** of the tongue.

III. ALIMENTARY CANAL DIVISIONS

Divisions of the alimentary canal are determined by the histophysiologic variations of the layers (Table 14.2). The alimentary canal has a general plan of histologic organization, in that the lumen is lined by a **mucosa**, composed of **epithelium**; a loose, cellular connective tissue known as the **lamina propria** housing glands; and the outer muscular layer of the mucosa known as the **muscularis mucosae**. The mucosa is surrounded

table 14.2 Selected Histologic Features of the Alimentary Canal

Region	Epithelium	Lamina Propria	Layers of MM*	Submucosa	Layers of Muscularis Externa†
Esophagus	Stratified squamous	Esophageal cardiac glands	Longitudinal	Collagenous CT, esophageal glands proper	Inner circular, outer longitudinal
Stomach	Simple columnar, no goblet cells	Gastric glands	Inner circular, outer longitudinal, sometimes outermost circular	Collagenous CT, no glands	Inner oblique, middle circular, outer longitudinal
Small intestine	Simple columnar with goblet cells	Villi, crypts of Lieberkühn, Peyer patches in ileum (extend into submucosa), lymphoid nodules	Inner circular, outer longitudinal	Fibroelastic CT, Brunner glands in duodenum	Inner circular, outer longitudinal
Large intestine, cecum, colon	Simple columnar with goblet cells	Crypts of Lieberkühn (lack Paneth cells), lymphoid nodules	Inner circular, outer longitudinal	Fibroelastic CT, no glands	Inner circular, outer longitudinal (modified to form teniae coli)
Rectum	Simple columnar with goblet cells	Crypts of Lieberkühn (fewer but deeper than in colon), lymphoid nodules	Inner circular, outer longitudinal	Fibroelastic CT, no glands	Two layers: inner circular, outer longitudinal
Anal canal	Simple columnar cuboidal (proximal), stratified squamous nonkeratinized (distal to anal valves), stratified squamous keratinized (anus)	Sebaceous glands, circumanal glands, lymphoid nodules, rectal columns or Morgagni (involve entire mucosa), hair follicles (anus)	Inner circular, outer longitudinal	Fibroelastic CT with large veins, no glands	Inner circular (forms internal anal sphincter), outer longitudinal
Appendix	Simple columnar with goblet cells	Crypts of Lieberkühn (shallow), lymphoid nodules (large, numerous, and may extend into the submucosa)	Inner circular, outer longitudinal	Fibroelastic CT, confluent lymphoid nodules, no glands, fat tissue (sometimes)	Inner circular, outer longitudinal

CT, connective tissue; MM, muscularis mucosae.
*The MM is composed entirely of smooth muscle throughout the alimentary canal.
†The muscularis externa is composed entirely of smooth muscle in all regions except the esophagus. The upper third of the esophageal muscularis externa is all skeletal muscle; the middle third is a mixture of skeletal and smooth muscle; and the lower third is all smooth muscle.

by a denser connective tissue, the **submucosa** that houses glands in two regions of the alimentary canal, namely the esophagus and the duodenum. The submucosa is surrounded by the **muscularis externa**, which, in turn, is covered either by a **serosa** or an **adventitia**. Variations of the components of these layers permit regional structural and functional specialization of the alimentary canal. Innervation of the alimentary canal is accomplished by the **enteric nervous system** (whose neurons are located in **Meissner** [**submucosal**] and **Auerbach** [**myenteric**] **plexuses**). The function of the enteric nervous system is modified by the **sympathetic** and **parasympathetic** components of the **autonomic nervous system**.

A. The esophagus is lined by a *stratified squamous nonkeratinized epithelium*. Its lamina propria, containing mucus-secreting **esophageal cardiac glands**, is surrounded by the **muscularis mucosae**, which varies in thickness and is composed of a single longitudinal layer of smooth muscle.

1. The submucosa houses mucus-secreting **esophageal glands proper**.
2. The upper third of the **muscularis externa** is composed only of **skeletal muscle**; the middle third is composed of a combination of **smooth and skeletal muscle**; and the lower third is composed only of **smooth muscle**. The striated muscles are controlled by the **vagus nerve** (**CN X**), whereas the smooth muscles are controlled by nerve fibers derived from the enteric nervous system.
3. The **muscularis externa** of the esophagus conveys a **bolus** of food from the pharynx into the stomach by **peristaltic activity**. Two physiologic **sphincters** (the pharyngoesophageal and the gastroesophageal) in the muscularis externa ensure that the **bolus** is transported in one direction only, toward the stomach.

B. The stomach acidifies and converts the bolus into a thick, viscous fluid known as *chyme*. It also produces **digestive enzymes** and **hormones**.

1. It exhibits longitudinal folds of the mucosa and submucosa (called **rugae**), which disappear in the distended stomach. The gross anatomy of the stomach is divided into four regions (cardiac, fundic, body, and pyloric), but, histologically, the stomach is said to have only three regions, the **cardiac region** (**cardia**), where the esophagus joins the stomach; the bulk of the stomach, composed of the fundus and body, is histologically identical, and therefore histologists refer to it as the **fundic region** (**fundus**); and the **pyloric region** (**pylorus**), where the stomach joins the small intestine.
2. The lining of the stomach has many well-like openings, known as **gastric pits** (**foveolae**), which are shallowest in the cardia and deepest in the pylorus (Fig. 14.2). The gastric glands of the stomach mucosa deliver their secretions into the bases of the gastric pits.

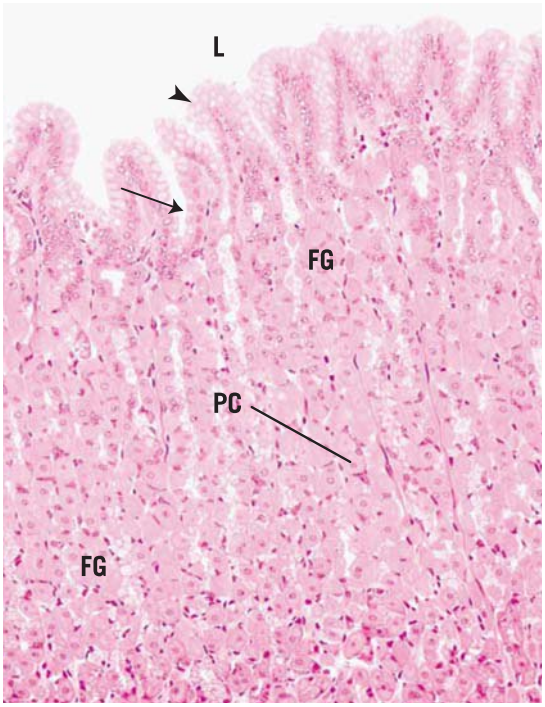


FIGURE 14.2. The gastric pits (*arrow*) of the fundic region of the stomach open into the lumen of the stomach (L), which is lined by mucus-producing surface lining cells (*arrowhead*). The lumina of the fundic glands (FG) open into the bottom of the gastric pits. Observe the large parietal cells (PC) that abound in the fundic glands (×132).

a. The **simple columnar** epithelium of the **gastric mucosa** is composed of mucinogen-producing **surface lining cells** (see Fig. 14.2). Although they are ***not*** goblet cells, they produce a thick, viscous mucus, known as **visible mucus**, that lines the epithelial lining of the stomach and protects it from the highly acidic chyme and, therefore, from autodigestion. It also houses a very small number of taste cells that, similarly to the taste buds of the tongue, are capable of recognizing the taste sensations, especially bitter, umami, and sweet. These cells are described more fully in the section on the small intestine. The **lamina propria** is a loose connective tissue housing smooth muscle cells, lymphocytes, plasma cells, mast cells, and fibroblasts. It contains **gastric glands**. The **muscularis mucosae** is composed of a poorly defined inner circular layer, an outer longitudinal layer, and occasionally an outermost circular layer of smooth muscle.

b. The **gastric submucosa** is composed of dense, irregular **collagenous** connective tissue housing fibroblasts, mast cells, and lymphoid elements embedded in the connective tissue. Additionally, the submucosa contains the **Meissner** (**submucosal**) **plexus** as well as arterial and venous plexuses that, respectively, supply and drain the vessels of the mucosa.

c. The **gastric muscularis externa** is composed of **three layers** of smooth muscle: an incomplete inner oblique layer, a thick middle circular layer that forms the **pyloric sphincter**, and an outer longitudinal layer. The **Auerbach myenteric plexus** is located between the middle circular and outer longitudinal smooth muscle layers. The gastric muscularis externa is responsible for mixing of gastric contents and emptying of the stomach and is affected by various characteristics of the chyme (e.g., lipid content, viscosity, osmolality, caloric density, and pH), which influence both the **emptying rate** of the stomach and the rate of muscle contraction.

d. The **serosa** covers the external surface of the stomach.

3. Gastric glands are simple branched tubular glands in the lamina propria of the **cardia**, **fundus**, and **pylorus**. Each gland consists of an **isthmus**, which connects the gland to the base of a gastric pit; a **neck**; and a **base** which extends to the muscularis mucosae.

a. Cells of the fundic glands

(1) Parietal (**oxyntic**) **cells** (see Fig. 14.2) are pyramidal cells concentrated in the upper half of the gland. They secrete **hydrochloric acid** (**HCl**) and **gastric intrinsic factor**. The latter is necessary for absorption of vitamin B_{12} in the ileum. These cells possess a unique intracellular **tubulovesicular system**, many mitochondria, and secretory **intracellular canaliculi** (deep invaginations of the apical plasma membrane) lined by **microvilli**.

(a) When the parietal cells are stimulated to secrete HCl, the number and length of microvilli increase and the complexity of the tubulovesicular system decreases (suggesting that tubulovesicular membranes are incorporated into the intracellular canaliculi, thus lengthening the microvilli).

(2) Chief (**zymogenic**) **cells**, pyramidal cells residing in the lower half of the **gland**, secrete **pepsinogen** (a precursor of the enzyme **pepsin**) and the precursors of two other enzymes, **rennin** and **lipase**. These cells display an abundance of basal rough endoplasmic reticulum (RER), a supranuclear Golgi complex, and many apical zymogen (secretory) granules.

(3) Mucous neck cells, located in the neck of the gland, possess short microvilli, apical mucous granules, a prominent Golgi complex, numerous mitochondria, and some basal RER. These cells may be able to divide. They produce **soluble mucus**, a slippery substance that lubricates the lining of the stomach.

(4) Diffuse neuroendocrine system (**DNES**) **cells** are of two major categories, **open** and **closed**. The DNES cells of the open category have short processes that reach the lumen; they are believed to be chemosensory and test the luminal content to release specific substances based on the circumstances. DNES cells of the closed category do not have processes that reach the lumen and, therefore, are "closed off" from the luminal content.

(a) DNES cells include more than a dozen types of cells that house many small hormone-containing granules, usually concentrated in the **basal** cytoplasm. Each particular enteroendocrine cell is believed to secrete only one hormone (Table 14.3).

(b) These cells possess an abundance of mitochondria and RER and a moderately well-developed Golgi complex.

(5) Regenerative cells are located primarily in the neck and isthmus; they replace all the epithelial cells of the gland, gastric pit, and luminal surface.

table 14.3 Selected Hormones Secreted by DNES Cells of the Alimentary Canal

Hormone	Cell	Site of Secretion	Physiologic Effect
Cholecystokinin	I	Small intestine	Stimulates release of pancreatic enzymes, contraction of gallbladder (with release of bile)
Gastric inhibitory peptide	K	Small intestine	Inhibits gastric HCl secretion
Gastrin	G	Pylorus, duodenum	Stimulates gastric secretion of HCl, pepsinogen
Ghrelin	P/D_1	Stomach, pancreas	Produces hunger sensations by adjusting the muscle tone of the muscularis externa as the stomach expands so that the gastric intraluminal pressure remains unchanged
Glicentin	GL	Stomach to colon	Stimulates hepatic glycogenolysis
Glucagon-like peptide 1	GLP-1	Small and large intestines	Reduces appetite; inhibits glucagon secretion and stimulates insulin secretion
Glucagon-like peptide 2	GLP-2	Small and large intestines	Stimulates mitotic activity in the crypts of Lieberkühn
Glucagon	A	Stomach, duodenum	Stimulates hepatic glycogenolysis
Histamine	ECL	Stomach	Stimulates secretion of HCl
Leptin	Gr	Mostly by adipose cells	Inhibits sensations of hunger
Motilin	Mo	Small intestine	Increases gut motility
Neurotensin	N	Small intestine	Inhibits gut motility, stimulates blood flow to ileum
Oxyntomodulin	L	Small and large intestines	Increases energy consumption and reduces appetite
Peptide YY	L	Small and large intestines	Decreases gastric motility and reduces appetite
Secretin	S	Small intestine	Stimulates bicarbonate secretion by pancreas and biliary tract
Serotonin, substance P	EC	Stomach to colon	Increases gut motility
Somatostatin	D	Pylorus, duodenum	Inhibits nearby DNES cells
Urogastrone*		Duodenum (Brunner glands)	Inhibits gastric HCl secretion, enhances epithelial cell division
VIP	VIP	Stomach to colon	Increases gut motility, stimulates intestinal ion, water secretion

Some of these hormones also are secreted in other parts of the body and have additional physiologic effects.
A, α-cell-like cell; D, δ-cell-like cell; EC, enterochromaffin-like cell; G, gastrin-producing cell; GL, glicentin-producing cell; HCl, hydrochloric acid; Mo, motilin-producing cell; N, neurotensin-producing cell; S, secretin-producing cell; VIP, vasoactive intestinal peptide.
*Not produced by diffuse neuroendocrine system cell.

   b. **Cardiac and pyloric glands** are different from fundic glands in that they are coiled tubular mucus-secreting glands and lack chief cells.

4. **Gastric juice** contains water, HCl, mucus, pepsin, lipase, rennin, and electrolytes. It is **very acidic** (pH 2.0) and facilitates the activation of pepsinogen to pepsin, which catalyzes the partial hydrolysis of proteins.
5. **Regulation of gastric secretion** is effected by neural activity (vagus nerve) and by several hormones.
   a. **Gastrin** and **histamine**, released by enteroendocrine cells in the gastric and duodenal mucosa, together with acetylcholine released by parasympathetic nerve fibers of the vagus nerve, **stimulate HCl secretion**.
   b. **Somatostatin**, produced by enteroendocrine cells of the pylorus and duodenum, inhibits the release of gastrin and thus **indirectly inhibits HCl secretion**.
   c. **Urogastrone** (also known as **human epidermal growth factor**), produced by Brunner glands of the duodenum, and **gastric inhibitory peptide** along with **prostaglandins**, produced by enteroendocrine cells in the small intestine, **directly inhibit HCl secretion**.

C. Small intestine

1. **Overview**—the **small intestine** is approximately 7 m long and has three regions: the **duodenum** (proximal), **jejunum** (middle), and **ileum** (distal). The small intestine secretes several **hormones**; it continues and largely completes the **digestion** of foodstuffs and **absorbs** the resulting metabolites.
2. The **luminal surface** of the small intestine possesses plicae circulares, intestinal villi, and microvilli, which collectively *increase the luminal surface area by a factor of 400 to 600.*
   a. **Plicae circulares** (**valves of Kerckring**) are permanent spiral folds of the **mucosa** and **submucosa** that are present in the distal half of the duodenum, the entire jejunum, and the proximal half of the ileum. Plicae circulares *increase the surface area twofold to threefold.*
   b. **Intestinal villi** (Figs. 14.3 and 14.4) are permanent evaginations that possess, in their connective tissue core (lamina propria), numerous plasma cells and lymphocytes, fibroblasts, mast cells, smooth muscle cells, capillary loops, and a **single lacteal** (blind-ended lymphatic capillary). Villi *increase the surface area 10-fold.*
   c. **Microvilli** of the **apical** surface of the epithelial cells of each villus possess actin filaments that interact with myosin filaments in the terminal web. Microvilli *increase the surface area about 20-fold.*
3. The **mucosa** of the small intestine has three layers, the epithelium, the connective tissue lamina propria, and the muscularis mucosae.
   a. The **simple columnar epithelium** is composed of goblet cells, surface absorptive cells, and some DNES cells, both the open and closed types (see Fig. 14.4).
      (1) **Goblet cells** are **unicellular exocrine glands** that produce **mucinogen**, which accumulates in membrane-bounded granules, distending the **apical** region (**theca**) of the cell. After being released, mucinogen becomes hydrated and is thus converted to **mucin**, a thick, viscous substance that acts as a **protective coating** of the epithelial lining of the lumen. These cells have their nucleus and other organelles in the basal region (**stem**) of the cell. They increase in number from the duodenum to the ileum.
      (2) **Surface absorptive cells**, tall columnar cells (see Fig. 14.4) with numerous mitochondria, smooth endoplasmic reticulum (SER) and RER, and a Golgi complex, possess a layer of closely packed microvilli (**striated border**) on their free apical surface. These cells have a **glycocalyx**, which overlies the microvilli and binds various enzymes, including disaccharidases and dipeptidases. These cells have well-developed **tight junctions** and **zonulae adherentes**.

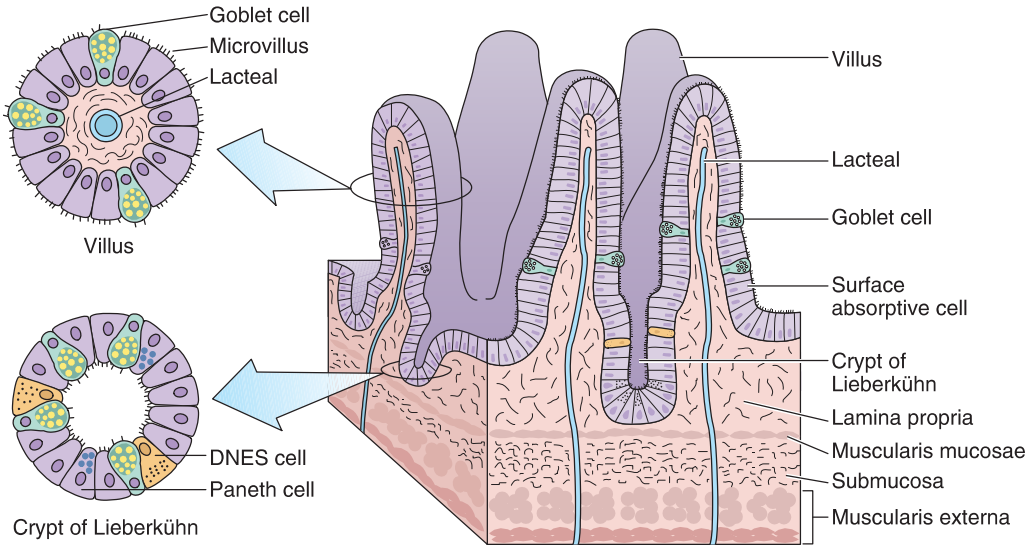


FIGURE 14.3. The spatial relationship of intestinal villi; crypts of Lieberkühn; and underlying muscularis mucosae, submucosa, and muscularis externa of the small intestine. Intestinal villi are evaginations of the epithelium and lamina propria. Each villus contains a single blind-ended lacteal and capillary loop. The submucosa, muscularis externa, and serosa are also depicted. DNES, diffuse neuroendocrine system.

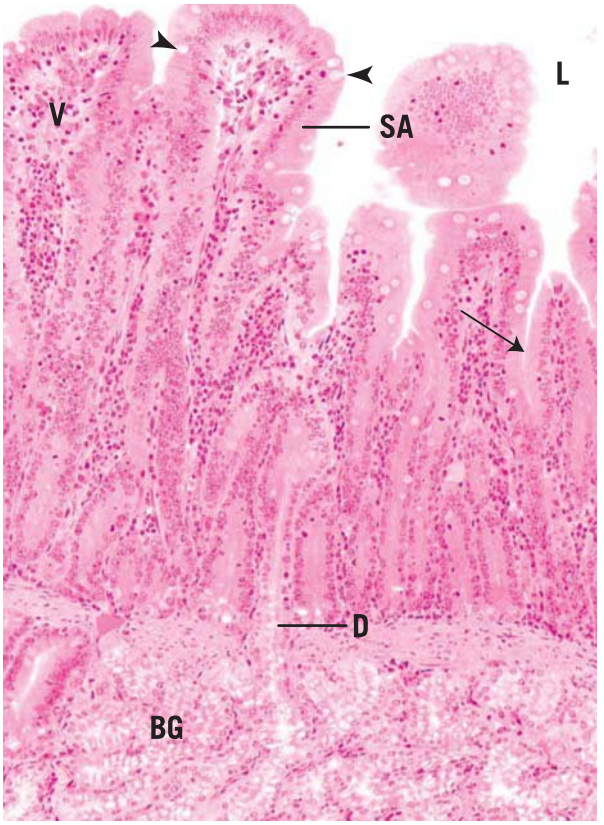


FIGURE 14.4. The villi (V) of the duodenum are covered mostly by surface absorptive cells (SA) as well as by goblet cells (*arrowheads*). The *arrow* is pointing to the approximate junction between the intervillar spaces that are continuous with the lumen (L) of the duodenum and the beginning of the crypts of Lieberkühn. The submucosa of the duodenum possesses Brunner glands (BG) whose ducts (D) open into the base of the crypts of Lieberkühn and, sometimes, into the intervillar spaces (×132).

(3) **DNES cells** produce and secrete **gastrin**, **cholecystokinin**, **gastric inhibitory peptide**, and several other hormones (Table 14.3). Some of the open DNES cells possess the three genes for G protein–linked taste receptors similar to those of the taste buds located on the tongue. As in taste buds, sweet taste is coded for by T1R2 and T1R3, bitter by two copies of T2R subtypes, and umami by T1R1 and T1R3. Importantly, the taste cells of the gastrointestinal (GI) tract communicate with the islets of Langerhans, signaling the β cells to release insulin once sweet taste is detected in the lumen.

b. The **lamina propria** occupies the cores of the villi and the interstices between the numerous **glands** (**crypts**) **of Lieberkühn** (see Figs. 14.3 and 14.4). It consists of loose connective tissue with lymphoid cells, fibroblasts, mast cells, smooth muscle cells, nerve endings, and **lymphoid nodules**, as well as **lacteals** (blind-ended lymphatic vessels) and **capillary loops**.

(1) **Crypts of Lieberkühn** are simple tubular glands that extend from the intervillous spaces to the muscularis mucosae of the intestine. They are composed of goblet and oligomucous cells, columnar cells (similar to surface absorptive cells), DNES cells, regenerative cells, Paneth cells, intermediate cells, and M cells (the last of this group, M cells, is discussed in Section III C 3 b **(2)**).

(a) **Paneth cells**, located at the base of the crypts of Lieberkühn, are pyramidal cells that secrete the antibacterial enzyme **lysozyme** stored in large, apical, membrane-bounded secretory granules. These cells also release other antibacterial agents, such as **defensins** and **tumor necrosis factor** α and display extensive RER (basally), a large supranuclear Golgi complex, and many mitochondria. These cells have the capability of killing bacteria as well as certain protozoa.

(b) **Regenerative cells**, located in the basal half of the crypts of Lieberkühn, are thin, tall, columnar **stem cells** that divide to replace themselves and the other types of epithelial cells.

(c) **Intermediate cells** make up the bulk of the epithelial lining of the crypts of Lieberkühn. These cells have regenerative properties; they are derived from regenerative cells but have not as yet committed themselves to a certain cell line.

(2) **Lymphoid nodules** are usually small and solitary and are located in the lamina propria of the duodenum and jejunum. They increase in size and number in the ileum, where they form large contiguous aggregates, known as **Peyer patches**, which frequently extend through the muscularis mucosae into the submucosa.

(a) **M (microfold) cells** are highly specialized, have an unusual shape, and lie in the epithelium over lymphoid nodules and Peyer patches. They are derived from undifferentiated cells of the crypts of Lieberkühn. These cells endocytose antigens as well as bacteria, viruses, and parasitic microorganisms. The endocytosed material is conveyed via transcytosis to macrophages and lymphocytes that lie in the infoldings of the basal plasmalemma of M cells. These macrophages and the B and T lymphocytes are actually located in the lamina propria.

(b) **Activated B lymphocytes** respond to antigenic challenge by forming more B cells, which enter the lymph and blood circulation, then return to their original locations, where they populate the lamina propria and differentiate into immunoglobulin A (IgA)-producing plasma cells.

(c) **Plasma cells** manufacture monomeric **IgA**. Two IgAs are bound to each other within the plasma cell by a protein, **protein J**, another product of the plasma cell, forming a dimeric variety of IgA. The IgA dimer then enters the lamina propria of the small intestine and binds to dimeric IgA receptors at the basal membrane of the surface absorptive cells. The **IgA-receptor complex** is endocytosed into the cell and is transported to an early endosome, to be transported across the intestinal epithelium (**transcytosis**) to the glycocalyx. Here a portion of the dimeric IgA receptor is cleaved from the complex, whereas the remainder of the receptor stays bound to the dimeric IgA as its secretory component, and the molecule is known as **secretory IgA** (**sIgA**). Some of the sIgA remains as an immunologic defense against bacteria and antigens in the lumen of the intestine. Much of the **sIgA** is reabsorbed by the surface absorptive cells and is transported into the lamina propria, where it enters blood vessels and goes to the liver; there, it is internalized by hepatocytes to be secreted as part of bile. From the liver, sIgA enters the gallbladder to be released into the lumen of the duodenum to join the sIgA already present there to contribute to the immunologic defense of the GI tract. This process of antibody transfer is referred to as the **enterohepatic circulation**.

c. The **muscularis mucosae** is composed of an inner circular and an outer longitudinal layer of smooth muscle.

CLINICAL CONSIDERATIONS

The immune system of the alimentary canal, under normal conditions, is tolerant of the normal bacterial flora and of epithelial cells lining the gut that are in close contact with bacteria. Researchers have demonstrated that this tolerance is due to dendritic cells (cells that act as antigen-presenting cells) that inhibit T cells from initiating an immune response. However, if the conditions become inimical to health, as in an inflammatory reaction, the dendritic cells instruct the T cells to respond and elicit an immune reaction. In order to assist the dendritic cells in their function of dictating tolerance, stromal cells of lymph nodes present proteins produced by cells of the alimentary canal to naïve T cells, instructing them to be tolerant of those proteins unless instructed otherwise by dendritic cells. Apparently, three types of dendritic cells are located in the lamina propria of the small intestine: conventional dendritic cells, plasmacytoid dendritic cells, and follicular dendritic cells; the first two of these interact with the enteric nervous system. Although the mechanism of interaction is not understood currently, these two types of dendritic cells seem to have receptors for a number of neurotransmitters, such as serotonin, vasoactive intestinal peptide, acetylcholine, dopamine, and glutamate, and these neurotransmitters can and do influence dendritic cells and their actions in immune responses. Moreover, dendritic cells reportedly have the ability to synthesize and release neurotransmitters, such as vasoactive intestinal peptide, serotonin, glutamate, and dopamine, suggesting that the interaction between dendritic cells and the enteric nervous system is a two-way process, whereby dendritic cells may modulate the functions of the enteric nervous system.

Tourists who have contracted the Shigatoxigenic group of *Escherichia coli* are at risk when they medicate themselves with antibiotics, such as ciprofloxacin, that they take on their trips as a protective measure to cure their diarrhea. Unfortunately, when these *E. coli* die, they release enormous quantities of the *Shiga* toxin that can kill the patient. Patients are advised not to take ciprofloxacin in case they have bloody diarrhea but rather to seek competent medical advice.

4. **Submucosa** of the small intestine consists of **fibroelastic** connective tissue containing blood and lymphatic vessels, nerve fibers, and **Meissner plexus.** It also houses **Brunner glands** (Fig. 14.4), which are present *only in the duodenum*. These glands produce an **alkaline fluid** and **urogastrone**. The former protects the duodenal epithelium from the acidic chyme; the latter is a polypeptide hormone (**human epidermal growth factor**) that enhances epithelial cell division and inhibits gastric HCl production.
5. The **muscularis externa** of the small intestine is composed of **two** layers of smooth muscle: an inner circular and an outer longitudinal layer. The inner layer participates in the formation of the **ileocecal sphincter**. **Auerbach** (**myenteric**) **plexus** is housed between the two layers.
6. **External layer of the small intestine**
   a. **Serosa** covers all of the jejunum and ileum and part of the duodenum.
   b. **Adventitia** covers the remainder of the duodenum.

D. Large intestine

1. **Overview**—the **large intestine** consists of the **cecum**, **colon** (ascending, transverse, descending, and sigmoid colon), **rectum**, **anal canal**, and **appendix**.
   a. The large intestine contains some digestive enzymes received from the small intestine, and it houses bacteria that produce **vitamin B_{12}** and **vitamin K**; the former is necessary for hemopoiesis and the latter for coagulation.
   b. The large intestine produces **abundant mucus**, which lubricates its lining and facilitates the passage and elimination of feces.
   c. **Function.** The large intestine functions primarily in the **absorption of electrolytes**, **fluids**, **and gases**. Dead bacteria and indigestible remnants of the ingested material are compacted into **feces**.
2. **Cecum and colon**
   a. The **mucosa of the cecum and colon lacks villi** and possesses no specialized folds. The **epithelium** is **simple columnar** with numerous goblet cells, surface absorptive cells, and occasional DNES cells.
      (1) The **lamina propria** is similar to that of the small intestine, possessing lymphoid nodules, blood and lymph vessels, and closely packed crypts of Lieberkühn, which lack Paneth cells.
         (a) **Fibroblasts** at the base of the crypts of Lieberkühn of the lamina propria undergo mitotic division and travel alongside the epithelial components of the intestinal crypt and, as they reach the vicinity of the opening of the crypt, differentiate into cells with characteristics of macrophages. These newly differentiated cells are thought to assist the monocyte-derived macrophages in their protective functions.
         (b) **Lymphoid elements**, members of the **gut-associated lymphoid tissues (GALT)**, composed of lymphoid nodules and cells, are richly represented in the lamina propria.
         (c) **Lymphoid drainage** occurs rarely, if ever, from the lamina propria; thus, the absence of lymphatic vessels greatly limits the capability of metastasis of malignant tumors from the mucosa of the colon.
      (2) The **muscularis mucosae** consists of an inner circular and outer longitudinal layer of smooth muscle cells.
   b. The **submucosa of the cecum and colon** is composed of **fibroelastic** connective tissue. It contains blood and lymphatic vessels, nerves, and the **Meissner** (**submucosal**) **plexus**.
   c. The **muscularis externa of the cecum and colon** is composed of an inner circular and a modified outer longitudinal layer of smooth muscle. The outer layer is gathered into three flat, longitudinal ribbons of smooth muscle that form the **teniae coli**. When continuously contracted, the teniae coli form sacculations of the wall known as **haustra coli**. **Auerbach** (**myenteric**) **plexus** is housed between the two layers of smooth muscle.
   d. **External layer of the cecum and colon**
      (1) Adventitia covers the posterior aspects of ascending and descending portions of the colon, whereas the anterior aspects (facing the peritoneum) are covered by serosa.
      (2) Serosa covers the cecum and the remainder of the colon. Fat-filled outpocketings of the serosa (**appendices epiploicae**) are characteristic of the transverse and sigmoid colon.
   e. The **lumen of the large intestine** houses trillions of microbes, approximately 10 times the number of cells in the entire human body. These microorganisms form a part of the body's **microbiome** whose physiologic balance has been shown to reflect the health of the individual harboring them. Three groups of intestinal flora, known as **enterotypes**, predominate in the

human population, and each individual possesses a predominance of one of these enterotypes. Although the epithelial lining of the colon has been shown to produce and release microRNAs into the lumen of the colon that apparently are able to control the gene activity of the resident microbes, how these enterotypes develop and their significance are not as yet understood.

CLINICAL CONSIDERATIONS

Malabsorption disorders may lead to malnutrition, resulting in wasting diseases, if major nutrients (carbohydrates, amino acids, ions) cannot be assimilated.

Gluten enteropathy (nontropical sprue, celiac disease) usually begins in childhood and results from the destructive effects of certain glutens (particularly of rye and wheat) on the villi of the small intestine, which reduce the surface area available for absorption. The symptoms include loss of appetite, abdominal bloating, and recurrent diarrhea (often bloody), and it is believed to be an autoimmune disease. Recently, infection with the retrovirus T1L during childhood has been shown to trigger an immune reaction by dendritic cells of the mesenteric lymph nodes against glutens. Currently, gluten enteropathy is treated by eliminating wheat and rye products from the diet, but vaccines against the T1L virus are hoped to eliminate the disease.

Malabsorption of vitamin B_{12} may cause pernicious anemia. It usually results from inadequate production of gastric intrinsic factor by the parietal cells of the gastric mucosa.

Cholera-induced diarrhea is caused by the action of cholera toxin, which blocks intestinal absorption of sodium ions and promotes excretion of water and electrolytes. It causes death shortly after onset unless the lost electrolytes and water are replaced.

Diverticulitis is a disease of the aging individual. As the person enters the fifth decade of life, the muscular layers of the large intestine begin to weaken, permitting the eventual formation of outpocketings (diverticula) of the mucosa and submucosa of the distal colon, mainly in the lower descending colon and the sigmoid colon. As materials become trapped in these diverticula, inflammation occurs in about 15% to 25% of individuals with diverticulosis; this inflammation is known as diverticulitis. Individuals suffering from diverticulitis exhibit abdominal pain (usually in the left lower quadrant of the abdomen), and, if the inflammation is severe, fever, nausea, diarrhea, and cramps may also be experienced.

Fecal transplant is a relatively recent procedure used in patients whose normal bacterial flora has been decimated and usurped by pathogenic bacteria, such as *Clostridium difficile*. These individuals suffer from *C. difficile* colitis with a resultant bout of diarrhea that may last as long as several months. Although these patients are placed on a long-term antibiotic regimen, in many cases, the colitis remains unresolved. Notably, if they receive a cleansing preparation such as the one used in preparation for a colonoscopy and then receive a fecal transplant from a healthy donor (usually a close member of the household), the colitis is resolved in a matter of days, the patient's intestinal flora returns to normal, and the diarrhea ceases.

Certain intestinal microbes have the ability to metabolize trimethylamine, a structure present in substances like carnitine of red meat and lecithin present in egg yolk, liver, wheat germ, and pork into **trimethylamine-*N*-oxide** (**TMAO**), a substance that increases the risk of atherosclerosis and stroke. In fact, blood TMAO level has been shown to be a relatively accurate indicator of impending heart attacks and strokes in individuals who otherwise display no risk factors for these conditions.

3. The **rectum** is similar to the colon but contains fewer and deeper crypts of Lieberkühn (see Table 14.2).
4. The **anal canal** is the constricted continuation of the rectum.
   a. The **anal mucosa** displays longitudinal folds called **anal columns** (or **rectal columns of Morgagni**), which join each other to form **anal valves**. The regions between adjacent valves are known as **anal sinuses**.
      (1) Epithelium of the anal canal is simple columnar changing to **simple cuboidal** proximal to the anal valves. It changes to **stratified squamous nonkeratinized** distal to the anal valves and to **stratified squamous keratinized** (epidermis) at the anus.

(2) The **lamina propria** is composed of **fibroelastic** connective tissue and contains sebaceous glands, circumanal glands, hair follicles, and large veins.
(3) The **muscularis mucosae** consists of an inner circular and an outer longitudinal layer of smooth muscle, both of which terminate at the anal valves.

b. The **anal submucosa** is composed of dense, irregular fibroelastic connective tissue that houses large veins.
c. The **anal muscularis externa** is composed of an inner circular and an outer longitudinal layer of smooth muscle. The inner circular layer forms the **internal anal sphincter**.
d. **Anal adventitia** attaches the anus to surrounding structures.
e. The **external anal sphincter** is composed of **skeletal muscle** whose superficial and deep layers invest the anal canal. It exhibits **continuous tonus**, thus maintaining a closed anal orifice. The degree of tonus is under **voluntary control**, so the retention or evacuation of feces normally can be controlled at will.

CLINICAL CONSIDERATIONS

Colorectal carcinoma is the second highest cause of cancer death in the United States (approximately 52,000 per year). It most commonly affects individuals who are 50 years or older, but its incidence has been increasing in adults who are young and middle aged. It usually arises from adenomatous polyps and may be asymptomatic for many years. Rectal bleeding is frequently present. Colorectal carcinoma is probably related to diet. Diets high in fat and refined carbohydrates and low in fiber appear to be associated with colorectal carcinoma.

Hemorrhoids are very common in people older than 50 years. They present as rectal bleeding during defecation. Hemorrhoids are caused by the breakage of dilated, thin-walled vessels of venous plexuses either above (internal hemorrhoids) or below (external hemorrhoids) the anorectal line.

Levator ani syndrome is a long-term, painful disorder because of sudden and prolonged contraction of the levator ani muscle. It is believed to be caused by inflammation in the pelvic floor or because of prolonged tension of the muscles in the region, and the pain could last as long as 15 to 20 minutes. The pain occurs most commonly in the sitting position and may be relieved by standing up or lying down. Treatments include physical therapy, mild electric stimulation administered intra-anally, and Botox injections administered on a regular basis.

5. **Appendix**
   a. The **appendix** is a short, tubular extension of the blind terminus of the cecum with a narrow, stellate, or irregularly shaped lumen that often contains debris. The wall of the appendix is **thickened** by large aggregates of **lymphoid nodules** in the mucosa and even in the submucosa (in middle-aged and older individuals) (Fig. 14.5).
   b. **Mucosa of the appendix**
      (1) The **epithelium** is **simple columnar** and contains surface absorptive cells and goblet cells.
      (2) The **lamina propria** displays **numerous lymphoid nodules** (capped by M cells) and lymphoid cells. It does not form villi but possesses **shallow crypts of Lieberkühn** with some goblet cells; surface absorptive cells; regenerative cells; occasional Paneth cells; and numerous DNES cells, especially deep in the crypts.
      (3) The **muscularis mucosae** is composed of an inner circular and outer longitudinal layer of smooth muscle.
   c. The **submucosa of the appendix** is composed of **fibroelastic** connective tissue containing confluent lymphoid nodules and associated cell populations.
   d. The **muscularis externa of the appendix** is composed of an inner circular and an outer longitudinal layer of smooth muscle.
   e. The **serosa** completely surrounds the appendix.

FIGURE 14.5. The histology of the appendix is similar to that of the colon, but it is smaller in diameter and has fewer crypts of Lieberkühn (*arrow*); its lumen (L) usually houses debris, and it is richly endowed with lymphoid elements with germinal centers (GC) and a corona (C). The muscularis mucosae (MM) is infiltrated by lymphocytes as is the submucosa (SM). Because this is an appendix from a human, the patient probably had appendicitis that would account for the great amount of lymphoid tissue (×270).

CLINICAL CONSIDERATIONS

The **function** of the appendix is not known, although recent studies demonstrated a very high concentration of bacterial biofilm in this small portion of the gut. Some have suggested that the appendix acts as a reservoir for the normal bacterial gut flora, and in the case of severe diarrhea, such as that caused by cholera toxins, when the normal bacterial population is decimated by the disease, reserve bacteria residing in the appendix are able to reestablish the normal intestinal flora.

Appendicitis, an inflammation of the appendix, is usually associated with pain and/or discomfort in the lower right abdominal region, fever, nausea, vomiting, and an elevated white blood cell count.

IV. DIGESTION AND ABSORPTION

A. Carbohydrates

1. **Salivary and pancreatic amylases** hydrolyze carbohydrates to **disaccharides** and **polysaccharides**. This process begins in the oral cavity, continues in the stomach, and is completed in the small intestine.
2. **Disaccharidases** present in the glycocalyx of the brush border of surface absorptive cells are cleaved into monosaccharides, principally into glucose, fructose, and galactose.
3. **Monosaccharides** are actively conveyed by transporters coupled to **Na^+** located at the microvillar bases into surface absorptive cells and then discharged by the use of additional transporters at the base of the cells into the lamina propria, where they enter the circulation to be transported to the liver via the **hepatic portal vein system**.

B. Proteins

1. **Pepsin** in the lumen of the stomach partially hydrolyzes proteins, forming a mixture of high-molecular-weight **polypeptides**. Pepsin activity is greatest at low pH.

2. **Pancreatic proteases** within the lumen of the small intestine hydrolyze the polypeptides received from the stomach into very short polypeptides (composed of no more than three or four amino acids) and dipeptides.
3. **Dipeptides** are cleaved into amino acids by dipeptidases present in the glycocalyx of the brush border of surface absorptive cells. Short polypeptides and amino acids are conveyed by transporters located at the base of the microvilli into surface absorptive cells. Amino acids and short polypeptides are discharged into the lamina propria by various transporters located at the base of the surface absorptive cells, where they enter the circulation to be transported to the liver via the **hepatic portal vein system**.

C. Fats are degraded by *pancreatic lipase* into *monoglycerides*, *free fatty acids*, and *glycerol* in the lumen of the small intestine (Fig. 14.6).

1. **Absorption of lipid digestion products** occurs primarily in the **duodenum** and **upper jejunum**.
   a. **Bile salts** act on the free fatty acids and monoglycerides, forming **water-soluble micelles**, which, along with **glycerol**, enter the surface absorptive cells.
2. **Formation of chyle**
   a. **Triglycerides** are resynthesized from monoglycerides and free fatty acids within the SER.
   b. **Chylomicrons** are formed in the Golgi complex by the complexing of the resynthesized triglycerides with proteins. Chylomicrons are transported to the lateral cell membrane and released by exocytosis; after crossing the basal lamina, they enter **lacteals** in the lamina propria to contribute to the formation of **chyle**.

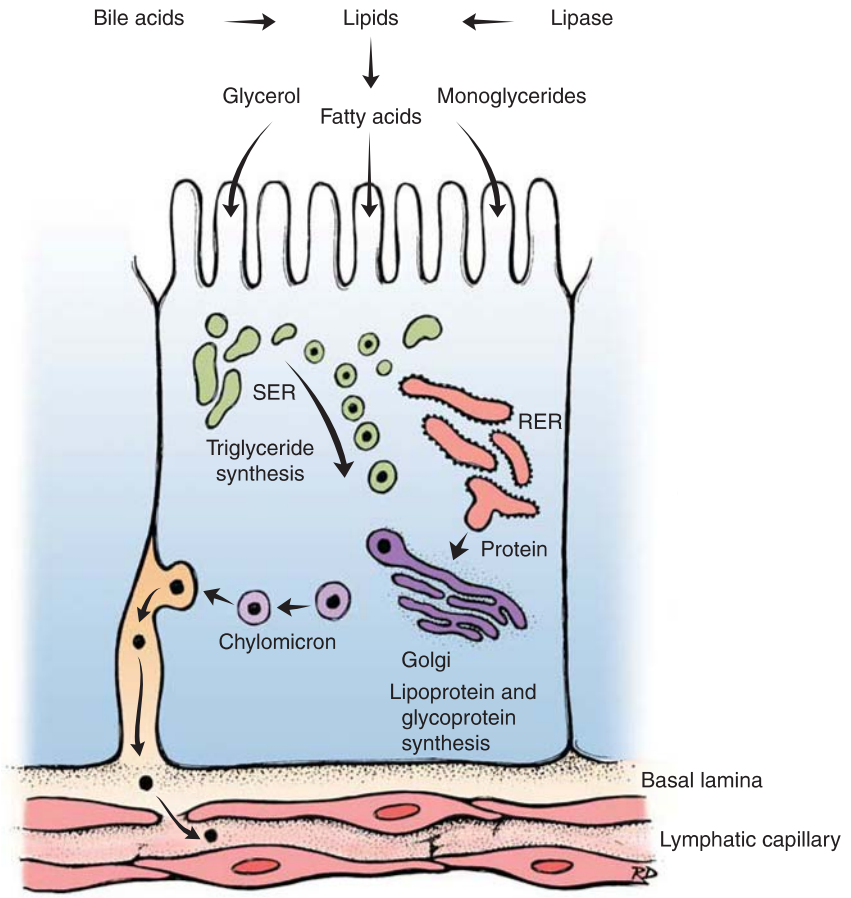


FIGURE 14.6. Absorption of lipids by surface absorptive cells of the small intestine and the formation of chylomicrons. RER, rough endoplasmic reticulum; SER, smooth endoplasmic reticulum.

c. **Chyle** enters the submucosal lymphatic plexus by contraction of smooth muscle cells in the intestinal villi.
d. The chyle travels via larger and larger lymph vessels into the largest lymph vessel, known as the **thoracic duct**, which empties into the junction of the left subclavian vein with the left internal jugular vein to enter the pulmonary circuit and finally enter into the **systemic circulation** at the left side of the heart.

3. **Short-chain fatty acids** of less than 10 to 12 carbon atoms are not reesterified but leave the surface absorptive cells directly and enter blood vessels of the lamina propria to be transported to the liver via the **hepatic portal vein system**.

D. Water and electrolytes are absorbed by surface absorptive cells of both the small and large intestine, whereas *gases* are absorbed mostly in the large intestine.

Review Test

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or completions of the statement. Select the ONE lettered answer that is BEST in each case.

1. A patient goes to the emergency department, and the physician notes one of the classic symptoms of appendicitis. Which of the following is that symptom?

(A) Apnea
(B) Vomiting of blood
(C) Depressed white cell count
(D) Rectal bleeding
(E) Lower right quadrant abdominal pain

2. A patient complains about two painful blisters near the midline of her upper lip. The examining physician observes that one of the blisters is oozing a clear fluid and the other is covered by a scab. What should be the diagnosis?

(A) Angular cheilitis
(B) Acne
(C) Infected sebaceous glands
(D) Herpetic stomatitis
(E) Mononucleosis

3. What is the role of fluoride in drinking water?

(A) Kills bacteria.
(B) Makes enamel crystals softer.
(C) Helps remineralizing enamel.
(D) Replaces calcium ions.
(E) Replaces phosphate ions.

4. The tolerance of the immune system to the normal bacterial flora is due to which of the following cells?

(A) B lymphocytes
(B) Plasma cells
(C) Eosinophils
(D) Mast cells
(E) Dendritic cells

5. A young child is brought to his pediatrician because he developed persistent diarrhea that is bloody occasionally, a bloated abdomen, and lack of appetite. What should the physician suspect?

(A) Cholera
(B) Celiac disease
(C) Diverticulitis
(D) Vitamin B_{12} malabsorption
(E) Shigatoxigenic *E. coli* infection

6. What is one of the treatment options for levator ani syndrome?

(A) Use of a laxative
(B) Use of a stool softener
(C) Botox injections on a regular basis
(D) Leg lift exercises
(E) Back muscle strengthening exercises

7. Alcohol enters blood stream from which structure of the digestive system?

(A) Oral cavity
(B) Pharynx
(C) Esophagus
(D) Stomach
(E) Duodenum

8. What characteristic is indicative of angular cheilitis?

(A) The patient is in his early 20s.
(B) The patient was positive for herpes virus.
(C) The patient has erythematous lesions at the corners of his mouth.
(D) The patient displays apnea.
(E) The patient has high blood levels of secretin.

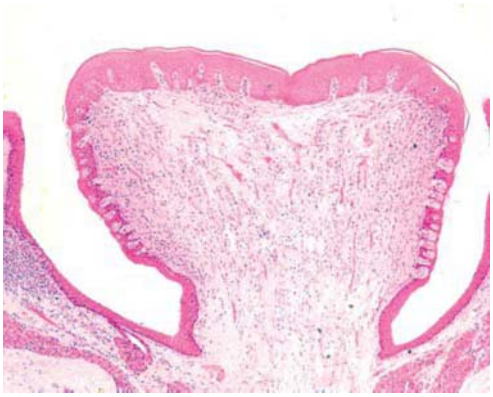
9. If odontoblasts malfunction because of developmental anomalies, which of the following will be affected?

(A) Cementum
(B) Enamel
(C) Dentin
(D) Tooth crown only
(E) Tooth root only

10. The photomicrograph above is from a healthy region of the biopsy of a patient with cancer. Where is the cancer located?

(A) Tongue
(B) Soft palate
(C) Hard palate
(D) Esophagus
(E) Colon

Question 10 is based on the photomicrograph below:



Answers and Explanations

1. **E.** Rectal bleeding or vomiting of blood often accompanies GI pathologies but not appendicitis. Elevated, not depressed, white cell count and abdominal pain are classic signs of appendicitis.
2. **D.** Herpetic stomatitis is caused by HSV type 1. In the dormant state, this virus resides in the trigeminal ganglia. HSV type 1 infection is very common and is transmitted by kissing. This infection is characterized by painful fever blisters on the lips or in the vicinity of the nostrils. These blisters exude a clear fluid or are covered by a scab.
3. **C.** The use of fluoride in the water supply to increase the fluoride concentration to 0.7 to 1.2 ppm (systemic application) makes enamel more resistant to bacterial acids by altering the hydroxyapatite crystals to fluoroapatite crystals (fluoride replaces hydroxyl molecules), making it less soluble by the acidic environment. Moreover, the presence of fluoride on the enamel surface catalyzes its remineralization and may decrease the ability of the resident bacteria to form organic acids.
4. **E.** The immune system of the alimentary canal, under normal conditions, is tolerant of the normal bacterial flora and of epithelial cells lining the gut that are in close contact with bacteria. This tolerance is due to dendritic cells (cells that act as antigen-presenting cells) that inhibit T cells from initiating an immune response. However, if the conditions become inimical to health, as in an inflammatory reaction, the dendritic cells instruct the T cells to respond and elicit an immune reaction.
5. **B.** Celiac disease usually starts in childhood and results from the destructive effects of certain glutens (particularly of rye and wheat) on the villi of the small intestine, which reduce the surface area available for absorption. The symptoms include loss of appetite, abdominal bloating, and recurrent diarrhea (often bloody), and it is believed to be an autoimmune disease.
6. **C.** Levator ani syndrome is a long-term, painful disorder because of sudden and prolonged contraction of the levator ani muscle. It is believed to be caused by inflammation in the pelvic floor or because of prolonged tension of the muscles in the region, and the pain could last as long as 15 to 20 minutes. The pain occurs most commonly in the sitting position and may be relieved by standing up or lying down. Treatments include physical therapy, mild electric stimulation administered intra-anally, and Botox injections administered on a regular basis.
7. **D.** Although most ingested food begins to be broken down in the stomach, in the small intestines, its digested components are absorbed to enter the blood stream. However, alcohol is one of the few substances that is absorbed by the stomach.
8. **C.** Angular cheilitis is a painful condition, usually in patients older than 50 years, in which the corners of the mouth have short erythematous fissures and cracks that are inflamed.
9. **C.** Dentin, present in both the crown and root of the tooth, is manufactured by odontoblasts.
10. **A.** The photomicrograph displays a circumvallate papilla, which is on the dorsum of the back of the anterior two-thirds of the tongue. Therefore, the biopsy was taken from the tongue.

chapter 15

Digestive System: Glands

I. OVERVIEW—DIGESTIVE SYSTEM EXTRINSIC GLANDS

The extrinsic glands of the digestive system include the **major salivary glands**, the **pancreas**, and the **liver** (with the associated **gallbladder**), all of which are outside the wall of the digestive tract. These glands produce enzymes, buffers, emulsifiers, and lubricants that are delivered to the lumen of the digestive tract via a system of ducts. They also produce hormones, blood proteins, and other products.

II. MAJOR SALIVARY GLANDS

A. Overview

1. The major salivary glands consist of three **paired exocrine** glands: the **parotid**, **submandibular**, and **sublingual glands**. These glands synthesize and secrete various products, such as secretory component, proteins, lysozyme, lactoferrin, thiocyanate, and salivary amylase.
   - **a.** The **secretory component** is a *portion* of the immunoglobulin A (**IgA) dimer receptor molecule** located on the basal plasma membrane of the secretory cell and facilitates the transfer of the IgA dimer, bound to the receptor, into the early endosome of the secretory cell. This portion of the receptor molecule remains bound to the IgA dimers, immunoglobulins that are produced by plasma cells in the connective tissue, forming a complex that resists enzymatic digestion in the saliva but can still perform its immune function.
   - **b.** The serous secretory cells of major salivary glands also secrete histidine-rich, proline-rich, and cysteine-rich **proteins**. The cells of the **striated ducts** of these glands also release the enzyme **kallikrein** both into the lumen and into the connective tissue. In the lumen, kallikrein begins the digestion of proline- and cysteine-rich proteins, whereas in the connective tissue, kallikrein enters the bloodstream, where it converts **kininogens** into the vasodilator and bronchial smooth muscle contractant **bradykinin**.
   - **c.** **Lysozyme**, **thiocyanate**, and **lactoferrin** are antimicrobial agents that control the bacterial flora of the oral cavity.
   - **d.** **Salivary amylase** begins the digestion of carbohydrates in the oral cavity.

B. The major salivary glands are *compound tubuloacinar* glands.

They are further classified as **serous**, **mucous**, or **mixed** (both serous and mucous), depending on the type of secretory acini they contain. These glands are surrounded by a capsule of dense irregular collagenous connective tissue with septa that subdivide each gland into lobes and lobules. Neurovascular elements serving these glands are conveyed to the acinar cells within the connective tissue septa. Autonomic innervation to the acini and ducts of salivary glands are responsible for controlling the release of saliva. Generally, the cholinergic (acetylcholine [ACh]-releasing) parasympathetic fibers induce the acinar cells to release their primary saliva. Some parasympathetic fibers release pituitary adenylate cyclase–activating polypeptide (PACAP), a neurohormone that induces saliva release from all three major salivary glands. The epidermal growth factor concentration has been shown to be increased in the saliva

table 15.1 Characteristics of the Major Salivary Glands

Salivary Gland	Weight (g)	Salivary Output (mL/day)	Type of Secretion	Duct Termination
Parotid	20–30	~300	Serous	Cheek into vestibule
Submandibular	10–12	~600	Mixed (mostly serous)	Sublingual papilla
Sublingual	2–3	~50	Mixed (mostly mucous)	Floor of the mouth

in the presence of PACAP. Sympathetic innervation, releasing noradrenaline, is responsible for the exocytosis of protein component of saliva by the acinar as well as by the duct cells.

1. **Salivary gland acini**
   - **a.** Salivary gland acini consist of pyramidal serous or mucous cells arranged around a central lumen that connects with an **intercalated duct**. Mucous acini may be overlaid with a crescent-shaped collection of serous cells called **serous demilunes**. Recently, researchers have suggested that serous demilunes are fixation artifacts, in that a mixed acinus has both serous and mucous cells situated around a central lumen. During processing for microscopy, the mucous cells become swollen and squeeze the bulk of the serous cells to the periphery of the acinus, making them appear to form a serous cap covering the mucous cells. If the tissue is flash-frozen, so that swelling of the mucous cells is prevented, serous demilunes are not present. In spite of this finding, and because serous demilunes are evident in nonfrozen preparations and classical histology uses these artifactual structures as classifying characteristics, in this review book, they will be treated as actual structures.
   - **b.** Acini of salivary glands possess **myoepithelial cells** that share the basal lamina of the acinar cells. The acinus and its associated intercalated and striated ducts form the **salivon**, the functional unit of a salivary gland.
   - **c.** The cells of the acinus release a **primary secretion** that resembles extracellular fluid. This secretion is modified in the ducts to produce the **final secretion**.
   - **d.** Salivary glands are classified according to their types of acini (Table 15.1):
     - **(1)** **Parotid glands** consist of **serous** acini and are classified as serous.
     - **(2)** **Sublingual glands** consist mostly of **mucous tubules** capped with **serous demilunes**. They are classified as mixed (Fig. 15.1).
     - **(3)** **Submandibular glands** consist of both **serous** and **mucous** acini (some also have serous demilunes). They are classified as mixed.
2. **Salivary gland ducts** are classified according to their size, location, and function.
   - **a.** **Intercalated ducts** originate in the acini and join to form striated ducts. They may deliver **bicarbonate ions** into the primary secretion.
   - **b.** **Striated** (**intralobular**) **ducts** are lined by **ion-transporting cells** that remove sodium and chloride ions from the luminal fluid (via a sodium pump) and actively pump potassium and bicarbonate ions into it, thus transforming the initial saliva (**primary saliva**) produced by the acinar cells into **secondary saliva**, which leaves the striated duct and eventually enters the oral cavity.
   - **c.** **Interlobular** (**excretory**) **ducts**, formed by the convergence of striated ducts, travel in connective tissue septa. These ducts drain into the **main duct** of each gland, which empties into the oral cavity.

C. Saliva is a *hypotonic* solution produced at the rate of about 1 L/d. It **lubricates** and **cleanses** the oral cavity by means of its water and glycoprotein content; **controls bacterial flora** by the action of thiocyanate, lysozyme, lactoferrin, and IgA, as well as by its cleansing action; initiates **digestion of carbohydrates** by the action of salivary amylase; acts as a solvent for substances that stimulate the taste buds; and assists in the process of deglutition (swallowing).

CLINICAL CONSIDERATIONS

The flow of saliva is important not only for the easy swallowing of masticated food and as a vehicle that facilitates the sensation of taste and the initiation of digestion but also for the maintenance of proper oral health. Individuals who had radiation treatment for cancers of the head and/or neck and those who are being treated with chemotherapy frequently have xerostomia (dry mouth) because of reduced salivary gland function. Frequently, these

patients have to use artificial saliva to maintain a moist oral environment. Usually, subsequent to the cessation of radiation therapy or chemotherapy, salivary gland function returns to normal.

Sjögren syndrome (**SS**) is an autoimmune disease with symptoms including xerostomia (dry mouth); dry eyes; and, generally, dry mucous membranes. It affects as much as 5% of the U.S. population and has an unequal gender distribution, affecting women nine times more frequently than men. Biopsies of salivary glands of patients with this condition display foci of lymphocytic infiltrates, increased ductal cell population, and decrease in the acinar cell population. Moreover, these patients are positive for serum autoantibodies for SS. Because about 60% of the patients also suffer from additional autoimmune diseases, such as systemic lupus, SS has been classified into two types: primary SS and secondary SS; those without additional autoimmune diseases are said to have primary SS. Although no cure exists for this painful and potentially debilitating disorder, eye drops, the frequent intake of fluids, and/or the use of artificial saliva relieve some of the symptoms.

Salivary calculus is a calcification that is formed usually in the parotid gland. It may block the flow of saliva through the parotid duct. Occasionally, the blockage results in the backflow of saliva, with a concomitant painful swelling of the parotid gland. Frequently, a simple massage of the parotid duct can dislodge the stone; otherwise, a surgical approach may be necessary.

Mumps, a contagious disease caused by the paramyxovirus, usually affects children 5 to 15 years of age but may affect adults as well. It is usually relatively benign in children, although it may cause considerable pain because of the swelling of the salivary glands (especially the parotids). In adult males, the virus may also cause swelling of the testes, and, in addition to the considerable pain, it may result in sterility if both testes are involved. In others, the pancreas may also become involved, causing pancreatitis with its attendant symptoms of abdominal pain and mild to severe nausea and vomiting. Fortunately, the symptoms subside within a week or so, with no residual complications. In a few adults, less than 10% of the cases, the mumps virus may also cause meningoencephalitis that resolves itself in a week or so, but in a very small number of cases, serious, life-long complications may result, including deafness and facial paralysis.

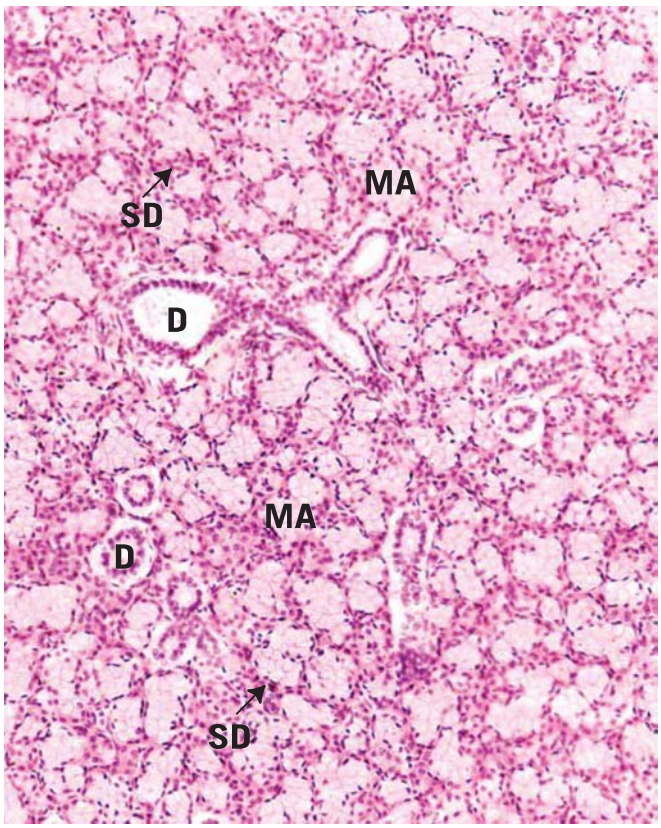


FIGURE 15.1. This is a low-magnification photomicrograph of a sublingual gland presenting its mucous acini (MA) and associated serous demilunes (SD). The ducts (D) of the submandibular gland are also prominent (×132).

III. PANCREAS

The pancreas has a slender connective tissue capsule. This gland produces **digestive enzymes** in its ***exocrine portion*** and a number of **hormones** in its ***endocrine portion*** (**islets of Langerhans**). Blood flow into the pancreas is arranged in such a fashion that the acini and the islets of Langerhans both receive arterial blood from vessels dedicated to these structures. Venous blood, drained from the islets of Langerhans, is delivered to the acini, so that hormones, such as somatostatin, released by those islet cells can reach the acinar cells immediately after release.

A. The exocrine pancreas is a *serous compound tubuloacinar* gland (Fig. 15.2).

1. **Pancreatic acinar cells**, pyramidal serous cells arranged around a central lumen, possess a round basal nucleus, abundant rough endoplasmic reticulum (RER), an extensive Golgi complex, numerous mitochondria, and many free ribosomes. Their basal plasmalemma has receptors for cholecystokinin (CCK) and acetylcholine (ACh).
   a. **Zymogen** (**secretory**) **granules** are membrane bound and densely packed in the **apical** region of pancreatic acinar cells. They contain enzymes and proenzymes packaged in the Golgi complex.
2. **Pancreatic ducts**
   a. The initial intra-acinar portion of the intercalated ducts is formed by **centroacinar cells**, which are low cuboidal with a pale cytoplasm.
   b. From the initial portion, the intercalated ducts converge into a small number of **intralobular ducts**, which, in turn, empty into large **interlobular ducts** that empty into the main (or accessory) pancreatic duct.
   c. The **main pancreatic duct** fuses with the common bile duct, forming the **ampulla of Vater**, which delivers secretions of the exocrine pancreas and the contents of the gallbladder into the duodenum at the **major duodenal papilla**.

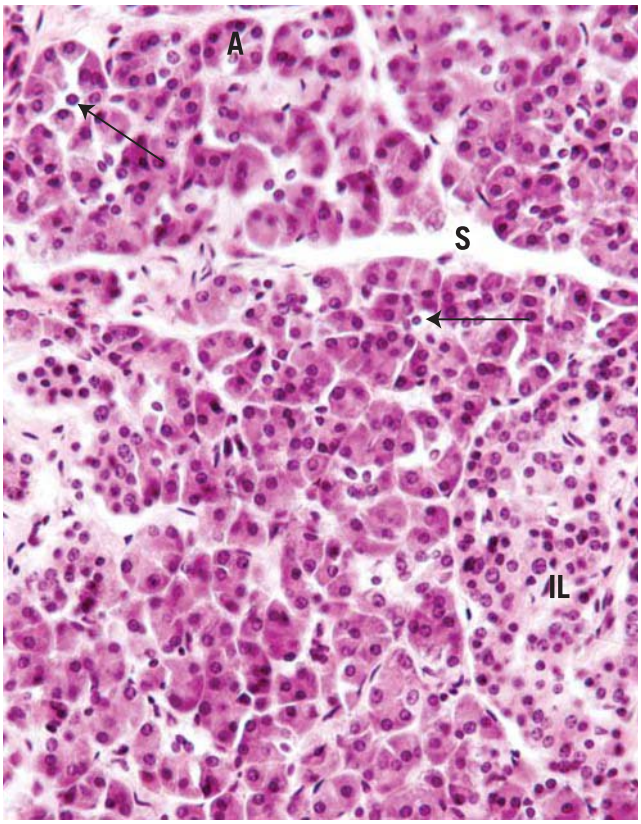


FIGURE 15.2. The islets of Langerhans (IL) represent the endocrine portion of the pancreas, whereas the acini (A), with their centroacinar cells (*arrows*), represent the exocrine portion of the pancreas. Observe the connective tissue septa (S) that subdivide the pancreas into lobes and lobules (×270).

table 15.2 Enzymatic Secretions of the Pancreas

Secretion	Type	Function
Pancreatic amylase	Enzyme	Acts on α-1,4-glycosidic bonds to catalyze the digestion of complex carbohydrate into simple sugars
Pancreatic lipases	Enzyme	Hydrolyzes triglycerides into free fatty acids and monoglycerides
Ribonuclease	Enzyme	An endonuclease that breaks phosphodiester bonds in both single- and double-stranded RNA into smaller RNA segments
Deoxyribonuclease	Enzyme	An endonuclease that breaks double-stranded DNA into smaller DNA fragments
Trypsinogen	Proenzyme	Its active form is the endopeptidase pancreatic trypsin, which is a serine protease that hydrolyzes proteins into small peptides
Chymotrypsinogen	Proenzyme	Its active form is serine protease, known as pancreatic chymotrypsin, which is a proteolytic enzyme that cleaves peptide bonds to hydrolyze proteins into small peptides
Procarboxypeptidase	Proenzyme	Its active form is protease pancreatic carboxypeptidase that cleaves peptide bonds at the "C-terminus" of proteins
Proelastase	Proenzyme	Its active form, pancreatic elastase, is a serine protease that functions in the breakdown of elastin into smaller peptide fragments

3. **Exocrine pancreatic secretions**
   a. **Enzyme-poor alkaline fluid** is released in large quantities by **intercalated duct cells** stimulated by **secretin** in conjunction with **ACh**. It probably **neutralizes** the acidic chyme as it enters the duodenum.
   b. **Digestive enzymes** are synthesized and stored in the pancreatic **acinar cells** (Table 15.2). Their release is stimulated by **CCK** (previously known as **pancreozymin)** and costimulated by ACh released by postganglionic parasympathetic fibers. These enzymes are secreted either as fully functional **enzymes** or as nonfunctional **proenzymes** that must be activated within the intestinal lumen.
      (1) Enzymes include pancreatic amylase, pancreatic lipases, ribonuclease, and deoxyribonuclease; **proenzymes** include trypsinogen, chymotrypsinogen, procarboxypeptidase, and proelastase.
      (2) In order to protect themselves from the digestive enzyme trypsin, these cells manufacture **trypsin inhibitor** so that trypsinogen cannot be converted to trypsin within the cytosol.

B. **Islets of Langerhans (endocrine pancreas) (see Fig. 15.2) are richly vascularized spherical clusters (100–200 μm in diameter) of endocrine cells surrounded by a fine network of *reticular fibers*.** They are scattered among the acini of the exocrine pancreas in an apparently random fashion. There are several types of **islet cells** but they can be differentiated from each other only by immunocytochemistry or by the use of special stains. These cells produce a number of polypeptide hormones, but *each cell type produces only one hormone.*
1. **Islet hormones** (Table 15.3)
   a. **Glucagon** is produced by **α cells** and acts to ***elevate the blood glucose level***.
   b. **Insulin** is produced by **β cells** and acts to ***decrease the blood glucose level***.
      (1) Mechanism of insulin release. Increased blood glucose levels cause glucose to bind to transmembrane proteins (**glucose transporter protein 2** [**GLUT-2**]) of β cells, which induces these cells to release their stored insulin and, if necessary, synthesize more insulin. This uptake of glucose occurs in a manner that does not require the presence of insulin.
      (2) Mechanism of insulin action. Insulin causes the transport of glucose and amino acids into hepatocytes, fat cells, cardiac muscle cells, and skeletal muscle cells. It does so by binding to the extracellular moiety of transmembrane insulin receptors of these cells, which triggers a response from the intracellular component that includes the placing of **GLUT-4** on the cell membranes of fat cells, skeletal muscle, and cardiac muscle cells, and glucose enters these cells by way of GLUT-4. Unlike in the case of GLUT-2, this uptake of glucose occurs in a manner that requires the presence of insulin.
   c. **Somatostatin** and **vasoactive intestinal peptide** (**VIP**) are produced by **δ cells** and **δ_1 cells** (**D cells** and **D_1 cells**), respectively. Somatostatin ***inhibits*** release of hormones by nearby secretory cells; it also inhibits the release of pancreatic enzymes and hydrochloric acid (HCl)

table 15.3 Comparison of Secretory Cells in Islets of Langerhans

Cell Type	Granule Characteristics	Relative Numbers	Location in Islets	Hormone	Function
Alpha (α)	Round; small halo between membrane and electron-dense core	~20%	Mostly at periphery	Glucagon	Elevate blood glucose levels
Beta (β)	Small; obvious halo between membrane, irregular dense core	~70%	Mainly central; present throughout	Insulin	Decrease blood glucose levels
Delta D cells (δ cells)	Both D and D_1 cells are large and electron lucent	<5%	Scattered throughout	Somatostatin	Inhibit hormone release by nearby cells; they also inhibit the release of pancreatic enzymes and HCl production by parietal cells in the stomach.
D_1 cells (δ_1 cells)				vasoactive intestinal peptide	Induce glycogenolysis; adjust gut motility and secretion of ions and water
Gastrin producing	Small	Rare	Scattered throughout	Gastrin	Stimulate HCl secretion
PP (F)	Small	Rare	Scattered throughout	Pancreatic polypeptide	Inhibit the release of exocrine pancreatic secretions as well as the release of bile from the gallbladder
Epsilon	Small	Rare	Scattered throughout	Ghrelin	Induce the feeling of hunger

HCl, hydrochloric acid; PP, pancreatic polypeptide-producing cells.

production by parietal cells in the stomach and ***reduces*** motility of the gastrointestinal (GI) tract and gallbladder by decreasing contraction of their smooth muscles. VIP ***induces*** glycogenolysis in the liver and adjusts gut motility and secretion of ions and water.

d. **Gastrin**, produced by **G cells**, ***stimulates*** (in conjunction with histamine and ACh) gastric HCl secretion.
e. **Pancreatic polypeptide**, produced by **PP cells**, ***inhibits*** release of exocrine pancreatic secretions and the release of bile from the gallbladder.
f. **Ghrelin**, produced by **epsilon cells**, produces the feeling of hunger.

CLINICAL CONSIDERATIONS

Individuals who have low blood glucose and high blood insulin levels may be suffering from **insulinoma**, a tumor of the β cells of the islets of Langerhans. Insulinomas are benign in 90% of the cases, and the condition is usually resolved by surgical excision of the tumor.

Type 1 (insulin-dependent) diabetes mellitus (IDDM) results from a **low level of plasma insulin** because of the autoimmune destruction of more than 80% of the insulin-producing β cells. It is characterized by **polyphagia** (insatiable hunger), **polydipsia** (unquenchable thirst), and **polyuria** (excessive urination). It usually has a **sudden onset** before 20 years of age and is distinguished by damage to and destruction of β cells of the islets of Langerhans. Because of its early onset, IDDM was also known as **juvenile-onset diabetes mellitus**, although **late-onset type 1 diabetes** can occur in adults. It is treated with a combination of insulin therapy and diet. Recent investigations using mice have shown that pancreatic acinar cells that were virally transfected with the gene for insulin can manufacture and release insulin in response to the presence of glucose. Studies using larger animals and, eventually, humans are planned for the near future.

Type 2 (non–insulin-dependent) diabetes mellitus does **not** result from low levels of plasma insulin and is **insulin resistant**, which is a major factor in its pathogenesis. The resistance to insulin is due to decreased binding of insulin to its plasmalemma receptors and to defects in postreceptor insulin action. It commonly occurs in overweight individuals older than 40 years and is usually controlled by diet, although it does occur with more and more frequency in young children. Frequently, patients are subscribed metformin, which not only facilitates a more normal response to insulin by cells but also decreases sugar absorption by the digestive tract and decreases gluconeogenesis by the liver.

Older individuals with type 2 diabetes often present with memory problems probably because amyloid β–derived diffusible ligands bind to the presynaptic membranes of the axons of certain neurons that are responsible for memory storage. This condition prevents the replenishment of insulin receptors of these axons, even though the receptors, synthesized in the soma, are available in the soma's cytoplasm. Apparently, the receptors are prevented from being transferred from the cytosol of the soma to the axoplasm of the axon. This makes these neurons insulin resistant and unable to regulate their glucose metabolism and in turn these neurons cannot function normally and the patient has memory loss and Alzheimer disease–associated dementia. Some researchers suggest this to be **type 3 diabetes.**

Monogenic diabetes is a very rare condition that involves less than 2% of people diagnosed with diabetes. This condition is almost always misdiagnosed as either type 1 or type 2 diabetes, but it is due neither to the destruction of β cells nor to the inability of somatic cells to respond to insulin; instead, this is a familial disease caused by a mutation in 1 of 20 or so genes, and the treatment is based on the particular gene that mutated. Proper diagnosis is aided by careful examination of patients with high blood glucose levels who do not exhibit the typical symptoms of diabetes, especially a fluctuating blood glucose level.

Pancreatic cancer is a malignant neoplasm, and most patients die within 6 months to 1 year after diagnosis. Most of the cases are **adenocarcinomas** in the head of the pancreas. Its incidence is three to four times greater in male patients than in female patients. Although its symptoms include anorexia, flatulence, fatty stool if the bile duct is obstructed, sudden loss of weight, weakness, back pain, and jaundice, exploratory biopsy is commonly required for a definitive diagnosis.

Blood glucose level in a fasting, nondiabetic individual should be between 80 and 110 mg/100 mL (4.4–6.1 mmol/L) of blood. If the glucose levels rise above that level, the β cells release insulin. If the blood glucose levels fall below that level, the α cells release glucagon. Additional control mechanisms include the neurotransmitters released by the cells of the autonomic nervous system, namely, sympathetic fibers increase glucagon secretion and inhibit insulin secretion, whereas parasympathetic fibers increase both insulin and glucagon secretions in order to maintain a balanced homeostasis.

IV. LIVER

A. Overview

1. The **liver**, the largest gland in the body weighing as much as 1.5 kg, is composed of a single type of parenchymal cell, the **hepatocyte**. It is surrounded by a dense, irregular collagenous connective tissue known as **Glisson capsule**, which gives rise to septa that subdivide the liver into its four lobes (right, left, caudate, and quadrate lobes) and its enormous number of lobules.
2. The liver produces **bile** and **plasma proteins** and has a myriad of other functions discussed below.

B. Light microscopic observation of the liver may be interpreted in three different ways, giving rise to three coexisting concepts of *liver lobules*: classic liver lobule, portal lobule, and acinus of Rappaport (Fig. 15.3).

1. The **classic liver lobule** is a hexagonal mass of tissue primarily composed of **plates of hepatocytes** (**liver cells**), which radiate from the region of the **central vein** toward the periphery (Fig. 15.4).
   a. **Portal areas** (**portal canals or portal triads**), regions of connective tissue between lobules that contain branches of the portal vein, hepatic artery, lymph vessel, and bile duct, are present at alternate corners of a classic liver lobule. Each portal area is surrounded by the **limiting plate**, a cylindrical plate of modified hepatocytes. A narrow space, known as the space of Moll, separates the limiting plate from the connective tissue elements of the portal area.
   b. **Liver sinusoids**, sinusoidal capillaries that arise at the periphery of a lobule and run between adjacent plates of hepatocytes, receive blood from the vessels in the portal areas and deliver it to the central vein. They are lined by **sinusoidal lining cells** (endothelial cells) that have large discontinuities between them, display **fenestrations**, and **lack basal laminae**. The lining of the sinusoid also contains **phagocytic cells** (**Kupffer cells**) derived from monocytes; these cells are interspersed among the sinusoidal lining cells but form no junctions with them; frequently

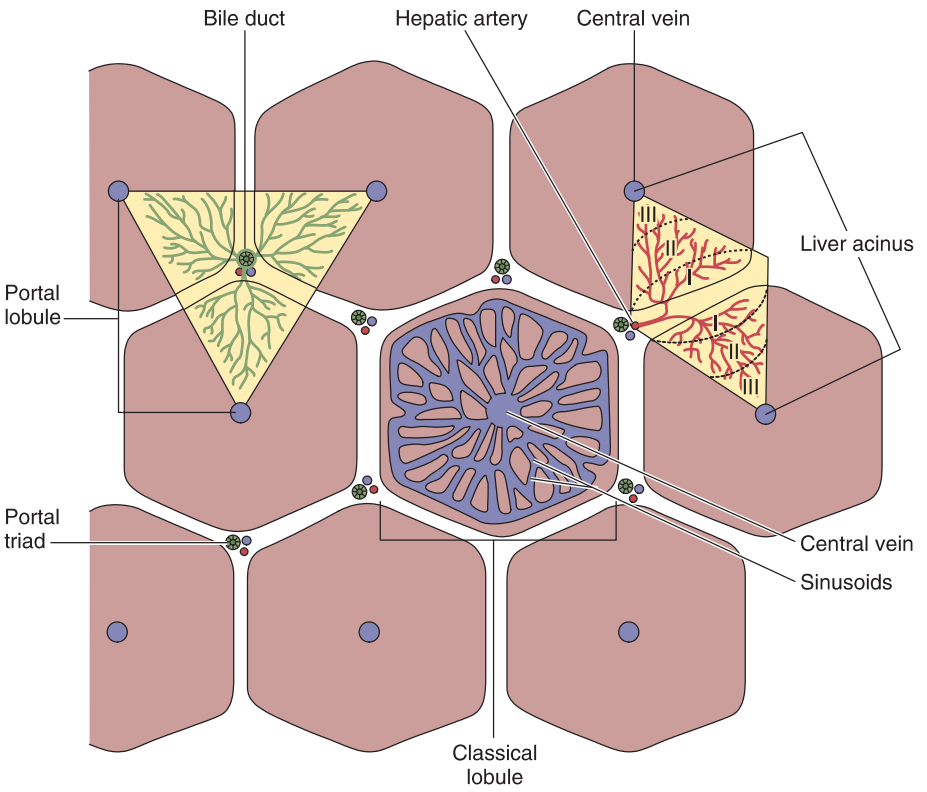


FIGURE 15.3. The defining characteristics of the classic liver lobule, portal lobule, and liver hepatic acinus of Rappaport. Observe the zonulation within the acinus of Rappaport. (Adapted with permission from Krause WJ, Cutts JH. *Concise Textbook of Histology*. 2nd ed. Baltimore, MD: Williams & Wilkins; 1986:331.)

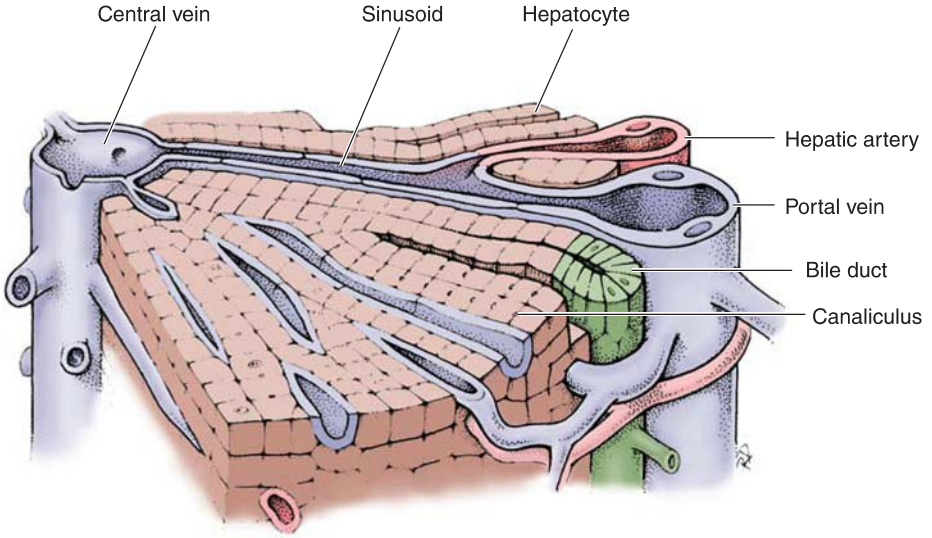


FIGURE 15.4. A portion of the classic liver lobule showing the area served by one portal triad.

they are located free within the sinusoid. Kupffer cells remove debris, old erythrocytes, and cellular fragments from the bloodstream.

c. The **space of Disse**, the **subendothelial space** between hepatocytes and the cells lining the sinusoids, contains the short microvilli of hepatocytes, reticular fibers (which maintain the architecture of the sinusoids), and occasional nonmyelinated nerve fibers. It also houses stellate-shaped **fat-storing cells** (**Ito cells** also known as **perisinusoidal stellate cells**), which preferentially store vitamin A. However, when the liver is compromised, hepatocytes release **tumor growth factor β**, and, in response, these fat-storing cells can divide, change their phenotype, and begin to synthesize collagen, leading to fibrosis and, if necessary, differentiate into **myofibroblasts** to control blood flow into the sinusoids. The space of Disse functions in the exchange of material between the bloodstream and hepatocytes. Hepatocytes do not directly contact the bloodstream.

2. The **portal lobule**, viewed in two dimensions, is a **triangular region** with three apices that are neighboring central veins and a center in a portal area (see Fig. 15.3). It contains portions of **three** adjacent classic liver lobules and is defined in terms of **bile flow**. In this concept of liver lobulation, the bile duct is in the center of the lobule.
3. The **hepatic acinus of Rappaport**, viewed in two dimensions, is a **diamond-shaped region** encompassing triangular sections of **two** adjacent classic liver lobules (with apices that are the central veins) and is divided by the common distributing vessels (see Fig. 15.3). This concept of liver lobulation is defined in terms of **blood flow** from the distributing vessels in a single portal area. This concept was established to explain the histologic appearance of pathologic changes that occur in liver disease. The hepatic acinus of Rappaport can be divided into **three zones** on the basis of the proximity of the hepatocytes to the incoming blood.

C. Blood, bile, and lymph flow (see Fig. 15.4)

1. **Blood flow into the liver** is derived from two sources and is directed from the portal triads at the periphery of each classic liver lobule toward the central vein. The **hepatic artery** brings oxygen-rich blood from the abdominal aorta and supplies 20% to 30% of the liver's blood. The **portal vein** brings nutrient-rich blood from the alimentary canal and spleen; it supplies 70% to 80% of the liver's blood.
2. **Blood flow out of the liver** occurs via the **hepatic vein**, formed by the union of numerous **sublobular veins**, which collect blood from the **central veins** (Fig. 15.5).
3. **Bile flow** is directed toward the periphery of the classic liver lobule (in the **opposite** direction of blood flow). Bile is carried in a system of ducts that culminate in the left and right **hepatic ducts**, which leave the liver and carry bile to the gallbladder.
   a. **Bile canaliculi** are expanded intercellular spaces between adjacent hepatocytes that form tiny canals for the initial flow of bile. They receive the liver's **exocrine secretion** (bile) and carry it to the **canals of Hering** (**bile ductules**) at the periphery of classic liver lobules. The canals of Hering are composed of both **modified hepatocytes** and low cuboidal-shaped **cholangiocytes** (**duct cells**). Cholangiocytes of the canals of Hering (or cells that resemble cholangiocytes and reside as cells of the canals of Hering) can act as regenerative cells both of the liver and of bile ductules and bile ducts. If even 50% of the liver is excised, it can regenerate to its previous size of 1.5 kg.
   b. **Bile ducts** receive bile from the canals of Hering; they are composed of a single layer of cuboidal-shaped cholangiocytes and are located in the portal areas. The apical surface of each cholangiocytes faces the lumen of the bile duct and displays numerous short microvilli as well as a single, long primary cilium that monitors bile flow and bile composition within the bile duct. These ducts enlarge and fuse with each other to form the **hepatic ducts**, composed of a stratified epithelium of cholangiocytes, which leave the liver at the porta hepatis.
4. **Lymph** in the liver collects in the space of Moll and is drained from there by branches of the lymph vessels located in the portal areas. As these lymph vessels coalesce, they increase in size and eventually form one or two larger lymph vessels that join the **thoracic duct** to return the lymph into the blood vascular system at the junction of the left subclavian and left internal jugular veins.

D. Hepatocytes are large polyhedral cells (20–30 μm in diameter) that possess abundant RER and smooth endoplasmic reticulum (SER); numerous mitochondria, lysosomes, and peroxisomes; several Golgi complexes; and many lipid droplets and glycogen deposits.

They usually contain one round

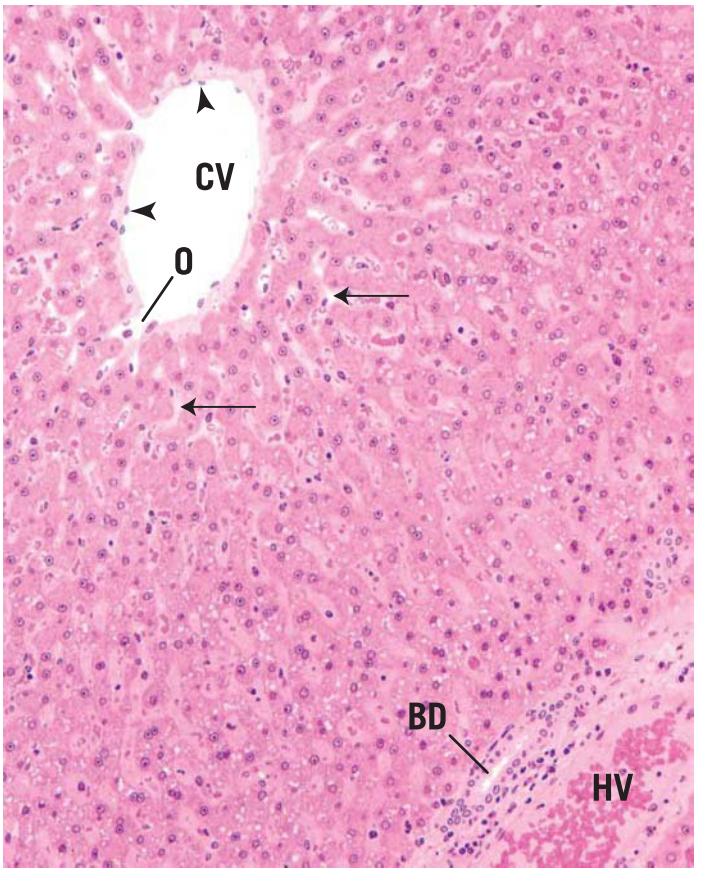


FIGURE 15.5. The central vein (CV) of the liver is lined by endothelial cells (*arrowheads*) that are continuous with those lining the liver sinusoid (*arrows*) where these sinusoids open (O) into the central vein. Observe the bile duct (BD) and a branch of the portal vein (HV) in a relatively large portal area (×132).

central nucleus; about 25% of the cells are binucleated but occasionally, nuclei are polyploid. The average lifespan of a hepatocyte is about 5 months.

1. **Hepatocyte surfaces**
   a. **Hepatocyte surfaces facing the space of Disse** possess microvilli, which by increasing the surface area facilitate the transfer of materials (e.g., endocrine secretions into the blood and nutrients into the hepatocytes) between the hepatocytes and the blood.
   b. **Hepatocyte surfaces abutting adjacent hepatocytes** frequently delineate bile canaliculi, small, tunnel-like expansions of the intercellular space. The **bile canaliculi** are sealed off from the remaining intercellular space by **occluding junctions** located on each side of each canaliculus. Plasma membranes of liver cells facing bile canaliculi have gap junctions and possess microvilli that extend into the bile canaliculus.

E. Liver functions carried out by hepatocytes include:

1. **Exocrine secretion** involves the production and release of 600 to 1,200 mL of **bile** per day. Bile is a fluid composed of water, bilirubin glucuronide (bile pigment), bile acids (bile salts), cholesterol, lecithin, phospholipids, ions, and IgA. Hydrophobic bilirubin, a breakdown product of hemoglobin, is converted into water-soluble bilirubin glucuronide (a nontoxic compound) in the SER of the hepatocytes.
2. **Endocrine secretion** involves the production and release of several **plasma proteins** (such as prothrombin, fibrinogen, albumin, factor III, and lipoproteins) and urea. Hepatocytes can also manufacture and release nonessential amino acids.
3. **Metabolites** are **stored** in the form of **glycogen** (stored glucose) and **triglycerides** (stored lipid).

4. **Gluconeogenesis** is the conversion of amino acids and lipids into glucose, a complex process catalyzed by a series of enzymes.
5. **Detoxification** entails the inactivation of various substances, such as drugs, noxious chemicals, and toxins. This is usually a two-step reaction:
   a. **Phase I** involves the cytochrome P450–dependent **microsomal mixed-function oxidase** systems that catalyze the oxidation and methylation of such substrates. These reactions usually occur in the SER or in peroxisomes, as in the case of alcohol.
   b. **Phase II** involves the conjugation of the resulting substances to endogenous cofactors such as acetyl coenzyme A, glutathione, sulfates, glucuronic acid to make them water soluble so that they can be excreted from the body.
6. **IgA transfer** involves the uptake of IgA across the space of Disse and its release into bile canaliculi. IgA is transported through the hepatobiliary duct system to the intestine, where it serves an immunologic protective function. This process is referred to as the **enterohepatic circulation**.

F. Hepatic functions carried out by cells other than hepatocytes:

1. **Ito cells** store vitamin A.
2. **Kupffer cells** phagocytose unwanted materials.

CLINICAL CONSIDERATIONS

Hepatitis is an inflammation of the liver, usually due to a viral infection, but occasionally due to toxic materials. A number of viruses can cause viral hepatitis, even cytomegalovirus and Epstein-Barr virus; however, the most common viral agents responsible for viral hepatitis are hepatitis A, B, C, D, and E viruses. Hepatitis B virus is a deoxyribonucleic acid (DNA) virus, and all the others are ribonucleic acid viruses. The most common symptoms of viral hepatitis are the obvious presence of jaundice and the elevated levels of serum alanine aminotransferase and serum aspartate aminotransferase in the blood.

Viral hepatitis A (**infectious hepatitis**) is caused by hepatitis A virus (HAV), which is frequently **transmitted by the fecal–oral route**. It has a **short incubation period** (2–6 weeks) and is usually not fatal but may cause jaundice. It is not transmitted by blood, it has no carrier state, and chronic liver disease is not one of the sequela. Annually, 1,780 new cases are reported in the United States.

Viral hepatitis B (**serum hepatitis**), caused by hepatitis B virus (HBV, a DNA virus), has a **long incubation period** (6 weeks–5 months). It is **transmitted by blood** and unprotected sex as well as from mother to newborn. Its clinical symptoms are similar to those associated with viral hepatitis A, but with more serious consequences, leading to a carrier state, chronic liver disease, cirrhosis, jaundice, and even death. The HBV sheds its DNA and may be detected in the patient's blood. Annually, 19,000 new cases of hepatitis B occur, resulting in 1,800 deaths in the United States.

Viral hepatitis C is caused by hepatitis C virus (HCV) and is responsible for most transfusion-related cases of hepatitis. It leads to chronic liver disease and cirrhosis and is also associated with **hepatocellular carcinoma**. It is usually transmitted by IV drug users who share needles and occasionally via unprotected sex. Annually, 16,500 new cases of hepatitis C are reported in the United States, with a total number of more than 3 million individuals infected with HCV.

Hepatitis D virus (HDV, also known as the **delta agent**) can replicate only in the presence of the HBV. It is transmitted by shared needles, blood, and unprotected sex. Its clinical symptoms are similar to those of viral hepatitis B, but with quicker onset.

Hepatitis E is caused by the hepatitis E virus (HEV) and is spread via the oral–fecal route and even from eating the undercooked meat of an infected animal. Common symptoms include jaundice, lethargy, weight loss, fever, muscle ache, nausea, dark urine, light-colored stool, and pain in the region of the liver. The disease is usually self-limiting, resolving itself about 2 months after the appearance of the symptoms.

Jaundice (**icterus**) is characterized by **excess bilirubin** in the blood and deposition of **bile pigment** in the skin and sclera of the eyes, resulting in a yellowish appearance. The urine has a dark color. Normal blood bilirubin level is less than 1.0 mg/dL, and an individual whose serum bilirubin level is greater than 2.5 mg/dL is considered to be jaundiced. It may be hereditary or caused by pathologic conditions, such as excessive destruction of red blood cells (**hemolytic jaundice**), liver dysfunction, and obstruction of the biliary passages (**obstructive jaundice**).

Reye syndrome is a very serious disorder in children that occurs when they receive aspirin during a viral infection. Children with this condition frequently become comatose, develop brain disorders and microvesicular steatosis, where hepatocytes accumulate small lipid droplets (about 1 μm in diameter) that may lead to temporary or permanent loss of function of those liver cells.

Alcoholic hepatitis is inflammation of the liver because of excessive alcohol consumption over an extensive period of time. Up to a certain extent, the condition is reversible; however, if the disease reaches a certain point, it may result in the death of the patient. If the condition is mild, the patient will display only elevated liver enzymes, but, if the condition is severe, the patient will exhibit jaundice; protracted prothrombin time; reduction in alertness and consciousness; extremely elevated liver enzymes; and, possibly, death.

Cirrhosis is the replacement of healthy liver tissue, usually, over a period of years by collagenous scar tissue. As the conditions that cause the death of liver cells persist, scar formation continues to increase, and the liver becomes less and less capable of performing its myriad of functions that are necessary to keep the patient alive. Cirrhosis cannot be cured, but its rate of development can be retarded by alleviating the causative factors. However, eventually, the liver will fail, and, without a liver transplant, the patient will succumb to the disease. The most common causes of cirrhosis are abuse of alcohol (about 25%), hepatitis B (about 25%) and C (about 25%), and nonalcoholic liver disease (a result of obesity, uncontrolled diabetes, uncontrolled hypertension, and hypercholesterolemia).

Portal hypertension, one of the vascular disorders of the liver, refers to increased blood pressure within the portal vein and its tributaries as a result of interference with the normal flow of blood through the liver. This interference can occur before the blood enters the liver (prehepatic), while the blood is within the liver (intrahepatic) or after the blood leaves the liver (posthepatic). Prehepatic causes are usually congenital malformation of the portal vein or obstruction of the portal vein and/or its tributaries (especially the splenic vein) by blood clots (thrombosis). The most frequent intrahepatic cause is vascular obstruction caused by cirrhosis or tumors; much less frequently, it is caused by vascular parasites, such as some species of *Schistosoma*. Posthepatic causes include congestion in the hepatic venous circulation because of congestive heart failure, tricuspid valve insufficiency, hepatic vein thrombosis, or neoplasms involving the hepatic vein system. The complications of portal hypertension include the development of collateral veins that become enlarged (formation of **varices**) in various regions whose blood enters the portal vein; these include the esophagus, stomach, intestines, and even the anus and rectum, where varices of the anal veins lead to hemorrhoids. If these varices burst, the blood may enter the lumen of the GI tract, resulting in blood in the feces (from the large intestine) or vomit (from the esophagus and/or stomach). Other complications may involve abdominal distension because of ascites, an accumulation of as much as 20 to 30 L of extracellular fluid within the peritoneal cavity. Once liver function is sufficiently compromised, other symptoms arise, including encephalopathy, thrombopenia, and leukopenia.

V. GALLBLADDER

A. **The gallbladder is a small oblong sac located on the inferior surface of the liver that can store as much as 70 mL of bile.** It has a single opening that communicates with the common hepatic duct via the **cystic duct**, which originates at the neck of the gallbladder. It has a muscular wall whose contraction, stimulated by **CCK** from diffuse neuroendocrine system cells of the duodenum in conjunction with ACh from the vagus nerve, forces bile from its lumen into the duodenum at the duodenal papilla. The wall of the gallbladder has four layers:

1. The **mucosa** is composed of a **simple columnar epithelium** and a richly vascularized lamina propria. When the gallbladder is empty, the mucosa displays highly convoluted folds (Fig. 15.6).
2. The **muscle layer** is composed of a thin, oblique layer of **smooth muscle cells**.
3. The **connective tissue layer** consists of dense irregular collagenous connective tissue and houses nerves and blood vessels.
4. The **serosa** covers most of the gallbladder, but adventitia is present where the organ is attached to Glisson's capsule of the liver.

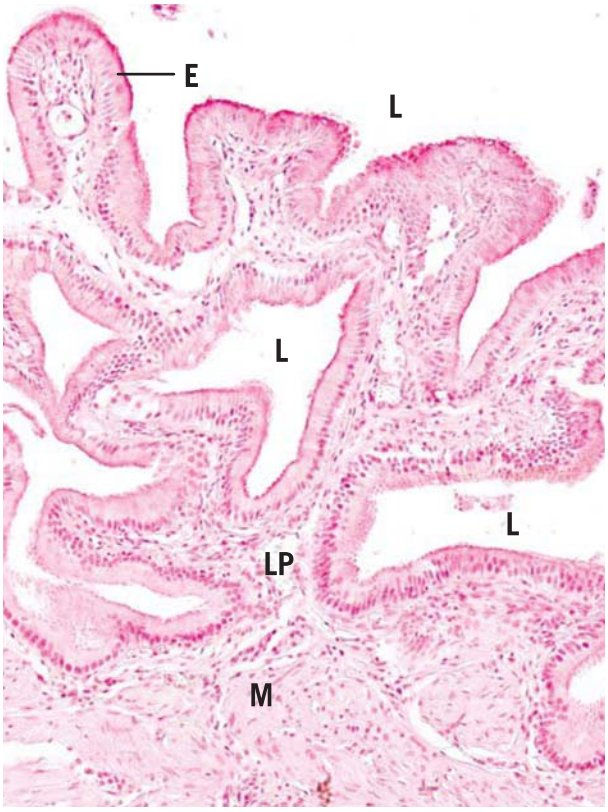


FIGURE 15.6. The mucosa of the empty gallbladder is highly folded, making the lumen (L) appear to be enclosed by the folds. The columnar epithelium (E) lining the lumen overlies a richly vascularized lamina propria (LP) that is surrounded by the smooth muscle (M) coat of the gallbladder (×132).

B. Function. The gallbladder concentrates, stores, and releases bile. It removes approximately 90% of the bile's water content by the manipulation of the subepithelial connective tissue electrolyte levels. It does so by actively removing sodium, chloride, and bicarbonate ions from the epithelial cells using energy-requiring pumps in the epithelial cell's basal plasmalemma, which in turn causes water to leave the cell, passively, via aquaporin 1 and aquaporin 8 channels. In order to equilibrate the osmotic differences between the bile in the lumen of the gallbladder and the epithelial cells lining the lumen, water moves from the bile into the epithelial cells because of the processes just described.

CLINICAL CONSIDERATIONS

Gallstones (**biliary calculi**) are concretions usually of fused crystals of **cholesterol**, which form in the gallbladder or bile duct. Accumulation of gallstones may lead to blockage of the cystic duct, which prevents emptying of the gallbladder, that has to be removed surgically if less invasive methods fail to dissolve or pulverize them.

Inflammation of the gallbladder, whether **chronic** or **acute**, usually due to the presence of gallstones obstructing the access to the cystic duct, is known as **cholecystitis**. Chronic cholecystitis is frequently the result of multiple bouts of acute cystitis. The acute form of the condition is quite painful, and the pain is experienced in the upper right quadrant of the abdomen and may be so severe as to induce nausea and vomiting. Frequently, the condition is treated by pulverizing the stones or surgically removing the gallbladder.

Review Test

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or completions of the statement. Select the ONE lettered answer that is BEST in each case.

1. An 18-year-old male feels faint and suffers from constant hunger, thirst, and excessive urination. What is the probable diagnosis?

(A) Viral hepatitis A
(B) Type 1 diabetes mellitus
(C) Type 2 diabetes mellitus
(D) Cirrhosis
(E) Mumps

2. A woman has yellow sclera and yellowish pallor. Blood test results indicate a low red blood cell count. What is the probable diagnosis?

(A) Viral hepatitis A
(B) Viral hepatitis B
(C) Cirrhosis
(D) Hemolytic jaundice
(E) Type 2 diabetes mellitus

3. A patient complains to her physician about sudden weight loss, loss of appetite, weakness, and back pain along with yellowish sclera and skin. What is the probable diagnosis?

(A) Type 2 diabetes
(B) Gallstones
(C) Pancreatic cancer
(D) Viral hepatitis A
(E) Viral hepatitis B

4. Which is the hepatitis virus that cannot replicate by itself?

(A) HAV
(B) HBV
(C) HCV
(D) HDV
(E) HEV

5. Which hepatitis virus has to be present to enable the other virus to replicate?

(A) HAV
(B) HBV
(C) HCV
(D) HDV
(E) HEV

6. A 45-year-old presents to the emergency room with abdominal pain; vomiting; and pain in his testicles, pancreas, and front of his ears. What is the probable diagnosis?

(A) Viral hepatitis A
(B) Viral hepatitis B
(C) Type 2 diabetes
(D) Cirrhosis
(E) Mumps

7. A female patient visits her ophthalmologist, complaining of dry eyes. Her ophthalmologist asks about additional symptoms and is told that the patient also has systemic lupus, dry mouth, and dryness in her vagina. What should the physician suspect?

(A) Sjorgen syndrome
(B) Pancreatic cancer
(C) Type 1 diabetes
(D) Cirrhosis
(E) Mumps

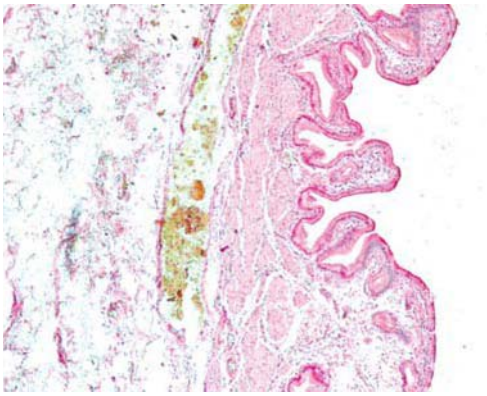
8. A patient who just moved to the East Coast from Colorado sees his physician for the first time and had a blood test 2 weeks prior to his appointment. The results were all within normal range except for his glucose level, which was much higher than normal. The patient told the physician that he always presents with same glucose level and has no other symptoms. What should the physician suspect?

(A) Type 1 diabetes
(B) Type 2 diabetes
(C) Type 3 diabetes
(D) Monogenic diabetes
(E) Insulinoma

9. What is the product of hepatocytes?

(A) Glucagon
(B) Lysozyme
(C) Insulin
(D) Plasma proteins
(E) Proteases

Question 10 refers to the photomicrograph below.



10. What was the patient who had surgery to remove this structure suffering from?

(A) Salivary calculi
(B) Cholecystitis
(C) Mumps
(D) Pancreatitis
(E) Portal hypertension

Answers and Explanations

1. **C.** The three classic signs of type 2 diabetes (juvenile onset) are polyphagia (excessive eating), polyuria (excessive urination), and polydipsia (excessive drinking). The condition occurs in young individuals, usually before 20 years of age.
2. **D.** Yellow skin and yellow sclera are indicative of jaundice. Because the patient had a low red blood cell count, the most probable diagnosis is hemolytic jaundice.
3. **C.** Pancreatic cancer has all of the symptoms listed, namely sudden weight loss, a loss of appetite, weakness, back pain, and jaundice. Although jaundice is noted in hepatitis A and B and in the presence of obstructive jaundice caused by gallstones, sudden weight loss, loss of appetite, and weakness are not diagnostic of these diseases. Diabetes mellitus does not cause jaundice, loss of appetite, or weight loss.
4. **D.** All of the hepatitis viruses can replicate by themselves, except for HDV.
5. **B.** HBV has to be present for HDV to be able to replicate.
6. **E.** In adult males, the virus may also cause swelling of the testes, and, in addition to the considerable pain, it may result in sterility if both testes are involved. In others, the pancreas may also become involved, causing pancreatitis with its attendant symptoms of abdominal pain and mild to severe nausea and vomiting.
7. **A.** SS is an autoimmune disease with symptoms including xerostomia (dry mouth); dry eyes; and, generally, dry mucous membranes. It affects as much as 5% of the U.S. population and has an unequal gender distribution, affecting women nine times more frequently than men.
8. **D.** Monogenic diabetes is a very rare condition that involves less than 2% of people diagnosed with diabetes. This condition is almost always misdiagnosed as either type 1 or type 2 diabetes, but it is due neither to the destruction of β cells nor to the inability of somatic cells to respond to insulin; instead, this is a familial disease caused by a mutation in 1 of 20 or so genes, and the treatment is based on the particular gene that mutated. Proper diagnosis is aided by careful examination of patients with high blood glucose levels who do not exhibit the typical symptoms of diabetes, especially a fluctuating blood glucose level.
9. **D.** Hepatocytes synthesize several plasma proteins, including fibrinogen, prothrombin, and albumin.
10. **B.** The photomicrograph is from a human gallbladder, and the patient had gallstones, which caused cholecystitis, inflammation of the gallbladder.

chapter **16**

Urinary System

I. OVERVIEW—URINARY SYSTEM

The **urinary system** is composed of the paired **kidneys** and **ureters** and the **bladder** and **urethra**; the kidneys produce and excrete **urine**, thereby clearing the blood of waste products. The kidneys also regulate the electrolyte levels in the extracellular fluid, synthesize renin and erythropoietin, and convert the less reactive form of vitamin D_3 (25-OH-vitamin D_3) to its more active form known as **calcitriol** [**1,25-$(OH)_2$ vitamin D_3**].

II. KIDNEYS

A. **Kidneys are paired bean-shaped organs enveloped by a thin *capsule* of connective tissue.** Each kidney, divided into an outer **cortex** and an inner **medulla**, contains about 1.3 million nephrons. A **nephron** and the **collecting tubule** into which it drains form the **uriniferous tubule**. Each collecting tubule drains a number of nephrons.

B. **The renal hilum is a concavity on the medial border of the kidney.** It houses arteries, veins, lymphatic vessels, nerves, and the renal pelvis.

C. **The renal pelvis (Fig. 16.1) is a funnel-shaped expansion of the upper end of the *ureter*.** It is continuous with the **major renal calyces**, each of which in turn has several small tributaries, the **minor calyces**.

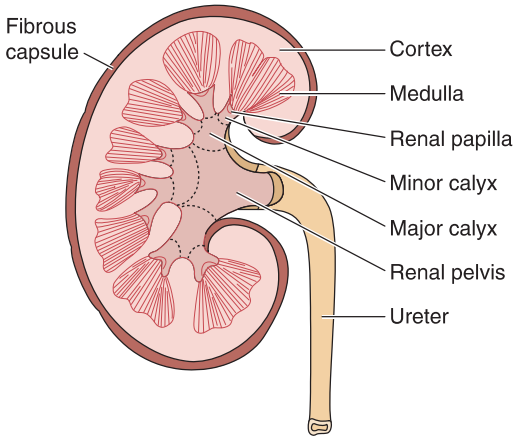


FIGURE 16.1. The internal structure of a bisected kidney.

D. The renal medulla lies deep to the cortex but sends extensions (*medullary rays*) into the cortex.

1. The 12 or more **renal (medullary) pyramids** are conical or pyramidal-shaped structures that compose the bulk of the renal medulla. The bases of the pyramids establish the corticomedullary junction. The apex of each pyramid forms the deepest portion of the medulla. Each pyramid consists primarily of the thin limbs of **loops of Henle**, blood vessels, and **collecting tubules**.
2. The **renal papilla**, located at the **apex** of each renal pyramid, has a perforated tip (**area cribrosa**) that projects into the lumen of a minor calyx.

E. The renal cortex, the superficial layer of the kidney beneath the capsule, consists primarily of *renal corpuscles* and *convoluted tubules*. Renal columns of Bertin are extensions of cortical tissue between adjacent renal pyramids, whereas **medullary rays** are groups of tubules that extend from the base of each renal (medullary) pyramid into the **cortex**. These tubules are the **straight portions** of the proximal and distal tubules as well as the **collecting ducts** that drain nephrons.

F. The renal lobe, consisting of a renal pyramid and its closely associated cortical tissue, is subdivided into renal lobules. Viewed in 2 dimensions, each renal lobule consists of a central medullary ray and the closely associated cortical tissue on either side of it, bounded on each side by an **interlobular artery**. Its many **nephrons** drain into the collecting tubules of the medullary ray.

G. The renal interstitium is the connective tissue compartment of the kidney. It is scanty in the cortex, occupying less than 10% of the cortical volume and somewhat greater in the medulla where it occupies about 20% of the medullary volume. The renal interstitium consists primarily of **fibroblasts** and **mononuclear cells** (probably macrophages). In the medulla, it consists of two additional cell types: **pericytes**, located along the blood vessels that supply the loops of Henle, and **interstitial cells** that have long **processes** that extend toward (and perhaps encircle) capillaries and tubules in the medulla. These cells manufacture the hormone **medullipin I** that is converted to **medullipin II** in the liver. Medullipin II is a vasodilator that acts to reduce blood pressure.

III. URINIFEROUS TUBULES (Table 16.1)

A. Nephrons consist of a *renal corpuscle*, a *proximal tubule* (composed of the *proximal convoluted tubule* and the *pars recta of the proximal tubule*), a *thin descending limb of the Henle loop*, a *Henle loop*, a *thin ascending limb of the Henle loop*, and a *distal tubule* (composed of the *pars recta of the distal tubule*, the very short *macula densa*, and the *distal convoluted tubule*). Unfortunately, the pars recta of the proximal tubule is also known as the **descending thick limb of the Henle loop**, and the pars recta of the distal tubule is also known as the **ascending thick limb of the Henle loop**.

1. Nephrons can be classified as **cortical**, **midcortical**, and **juxtamedullary**, depending upon the location of the renal corpuscle. The renal corpuscles of cortical nephrons are near the capsule, those of juxtamedullary nephrons are near the corticomedullary junction, and those of the midcortical nephrons are in between the other two. Juxtamedullary nephrons possess longer loops of Henle than do cortical or midcortical nephrons and are responsible for establishing the interstitial concentration gradient in the medulla. Even though only about 15% of all nephrons in humans are juxtamedullary nephrons, the ensuing description is of a juxtamedullary nephron because once its structure and function are understood, the structure and function of the other two nephron types become self-evident.
2. A **renal corpuscle** (Fig. 16.2) consists of the **glomerulus** and **Bowman capsule** and is the structure in which **filtration of blood** occurs.
   - **a. Bowman capsule**
     - **(1)** The **parietal layer** is the simple squamous epithelium that lines the outer wall of the Bowman capsule.
     - **(2)** The **visceral layer** (glomerular epithelium) is the modified simple squamous epithelium composed of **podocytes** that line the inner wall of the Bowman capsule and envelop the glomerular capillaries.

table 16.1 Important Structural and Functional Characteristics of the Uriniferous Tubule

Region	Epithelium	Major Functions	Summary
Renal corpuscle	Simple squamous epithelium lining Bowman capsule: podocytes (vistceral layer), outer (parietal layer)	Filters blood	Filtration barrier of fenestrated endothelial cells, fused basal laminae, filtration slits between podocyte secondary processes (pedicels)
Proximal convoluted tubule	Simple cuboidal epithelium with brush border; many compartmentalized mitochondria	Resorbs all glucose, amino acids, filtered proteins; at least 80% Na, Cl, H_2O	The activity of Na pumps in basolateral membranes, transporting Na^+ out of tubule, reduces volume of ultrafiltrate, maintains its isotonicity with blood
Loop of Henle, descending thick limb	Lined by simple cuboidal epithelium with brush border	Same as for proximal convoluted tubule	Same as for proximal convoluted tubule
Loop of Henle, descending thin limb	Simple squamous epithelium	Permeable to H_2O, which exits ultrafiltrate and enters interstitium; Na, Cl enter ultrafiltrate	Ultrafiltrate becomes hypertonic with respect to blood; urea, from interstitium, also enters lumen of tubule
Loop of Henle, ascending thin limb	Simple squamous epithelium	Somewhat permeable to H_2O, which enters ultrafiltrate from interstitium; Na, Cl exit ultrafiltrate	Ultrafiltrate remains hypertonic with respect to blood; urea, from interstitium, also enters lumen of tubule
Loop of Henle, ascending thick limb	Simple cuboidal epithelium; compartmentalized mitochondria	Impermeable to H_2O; Cl actively transported out of tubule into interstitium; Na follows	Ultrafiltrate becomes hypotonic with respect to blood; Cl pump in basolateral membranes is primarily responsible for establishing osmotic gradient in interstitium of outer medulla
JG apparatus macula densa	Simple cuboidal epithelium	Monitors level of Na (or decrease of fluid volume) in ultrafiltrate of distal tubule	Macula densa cells communicate with JG cells in afferent arteriole via gap junctions
JG cells in afferent arteriole	Modified smooth muscle cells containing renin granules	Cells synthesize renin, release it into bloodstream	Renin acts on plasma protein, to trigger events leading to formation of angiotensin II, release of aldosterone from adrenal gland
Distal convoluted tubule	Simple cuboidal cells; compartmentalized mitochondria	Cells respond to aldosterone by removing Na from ultrafiltrate	Ultrafiltrate more hypotonic in presence of aldosterone; K^+, NH_4^+, H^+ enter ultrafiltrate
Collecting tubules	Simple cuboidal epithelium; simple columnar epithelium	In absence of ADH, tubule impermeable to H_2O; hypotonic urine excreted	In presence of ADH, tubule permeable to H_2O, which is removed from filtrate, producing hypertonic urine

ADH, antidiuretic hormone; JG, juxtaglomerular.

(3) The **Bowman space** (also known as **capsular space** or **urinary space**) is the narrow chalice-shaped cavity between the visceral and parietal layers into which the ultrafiltrate passes.

(4) The **vascular pole** is the site on the Bowman capsule where the afferent glomerular arteriole enters and the efferent glomerular arteriole leaves the glomerulus.

(5) The **urinary pole** is the site on the Bowman capsule where the capsular space becomes continuous with the lumen of the proximal convoluted tubule.

b. **Podocytes** are highly modified epithelial cells that form the **visceral layer** of Bowman capsule and synthesize **glomerular endothelial growth factor**, a signaling molecule that facilitates the formation and maintenance of the glomerular endothelial cells. Podocytes have complex shapes and possess several **primary processes** that give rise to numerous secondary processes called pedicels.

(1) **Pedicels** embrace the glomerular capillaries and interdigitate with pedicels arising from other primary processes. Their surfaces facing Bowman space are coated with **podocalyxin**, a protein that is thought to assist in maintaining their organization and shape. Pedicels possess $\alpha_3\beta_1$ **integrin** molecules that cause them to adhere to the basal lamina.

(2) **Filtration slits** are elongated spaces about 40 nm in width between adjacent pedicels. A **filtration slit diaphragm** bridges each filtration slit and is the principal barrier responsible for the filtration of proteins.

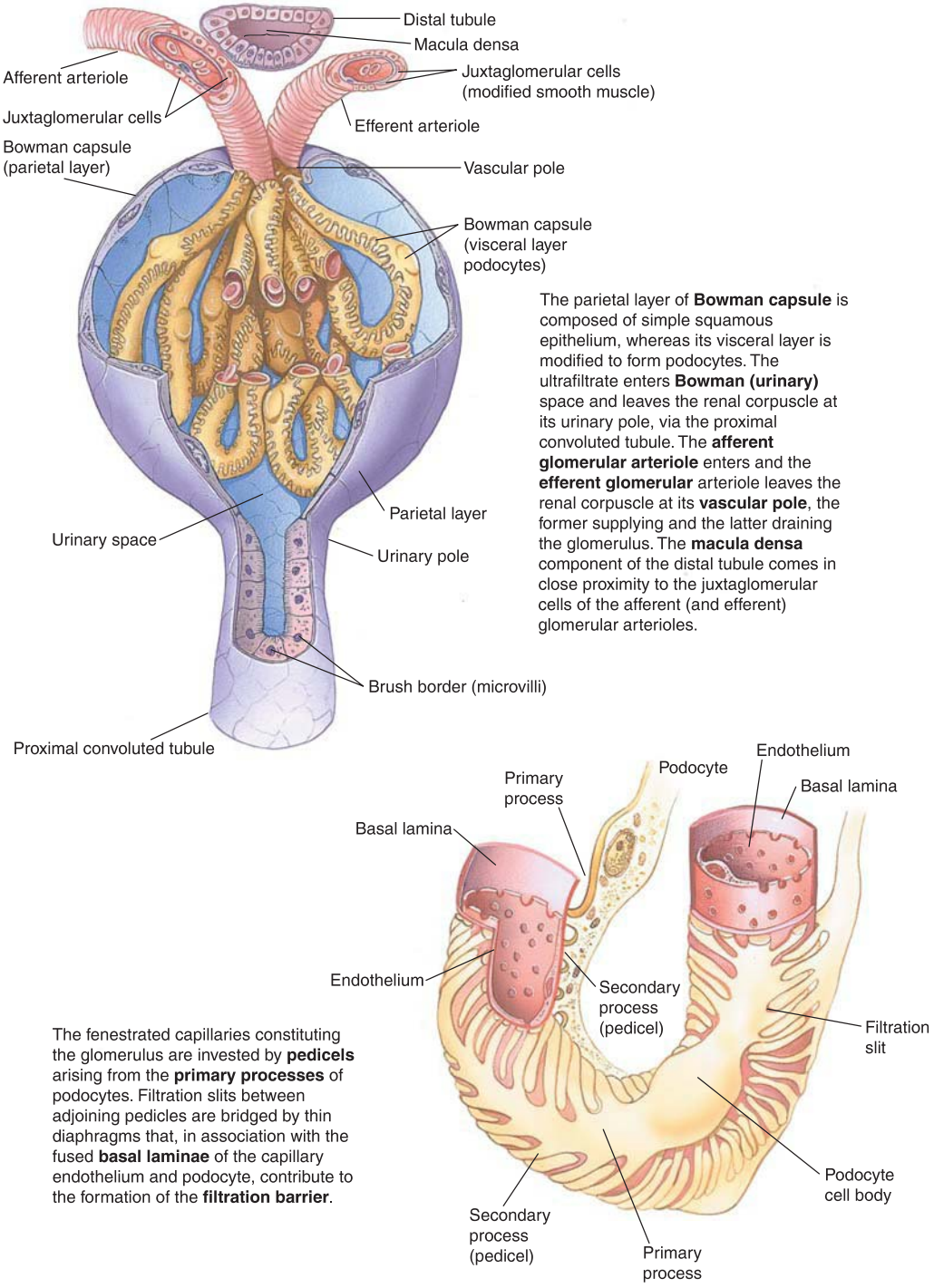


FIGURE 16.2. A diagram illustrating components of the renal corpuscle. (From Gartner LP. *Color Atlas of Histology.* 7th ed. Baltimore, MD: Wolters Kluwer; 2018:455.)

(a) Each slit diaphragm is composed of extracellular portion of the transmembrane protein **nephrin** of one pedicel that contacts the extracellular portion of nephrin from the adjacent pedicel. Within the cytoplasm of the pedicel, the intracellular moiety of

nephrin binds to **podocin** as well as to **CD2-associated proteins** that in turn bind to **actin filaments** and in that manner stabilize the nephrin molecule.

c. The **renal glomerulus** is the **tuft of capillaries** that extend into the Bowman capsule. Glomerular endothelial cells form the inner layer of the capillary walls. They have a thin cytoplasm that is thicker around the nucleus, where most organelles are located. These endothelial cells possess large **fenestrae** (60–90 nm in diameter) but **lack the thin diaphragms** that typically span the openings in other fenestrated capillaries.

(1) The **basal lamina** is interposed **between** the podocytes and the glomerular endothelial cells and is manufactured by **both** cell populations. It is unusually **thick** (0.15–0.5 μm) and contains three distinct **zones**. The **lamina rara externa**, an electron-lucent zone adjacent to the podocyte epithelium; the **lamina densa**, a thicker, electron-dense intermediate zone of amorphous material; and the **lamina rara interna**, an electron-lucent zone adjacent to the capillary endothelium.

(2) The **mesangium** is the interstitial tissue between glomerular capillaries. It is composed of mesangial cells and an amorphous extracellular matrix elaborated by these cells.

(a) **Mesangial cells** phagocytose large protein molecules and debris, which may accumulate during filtration or in certain disease states. They can also **contract**, thereby decreasing the surface area available for filtration. These cells **manufacture** platelet-derived growth factor, endothelins, interleukin-1, and prostaglandin E_2 and possess **receptors for angiotensin II** and **atrial** and **B-type natriuretic peptides**.

(b) The **mesangial matrix**, manufactured by mesangial cells, is composed of type IV collagen, laminin, and proteoglycans; it helps support glomerular capillaries.

d. The **renal filtration barrier** (Fig. 16.3) is composed of the **fenestrated endothelium** of the glomerular capillaries, the **basal lamina** (lamina rara and lamina densa), and the **filtration slit diaphragm** bridging the filtration slits between adjacent pedicels. It ***permits passage*** of water, ions, and small molecules from the bloodstream into the capsular space but ***prevents passage*** of large and/or most negatively charged proteins, thus forming an **ultrafiltrate of blood plasma** in the Bowman space.

(1) The **laminae rarae** contain **heparan sulfate**, a polyanionic glycosaminoglycan that assists in **restricting the passage of negatively charged proteins** into the Bowman space.

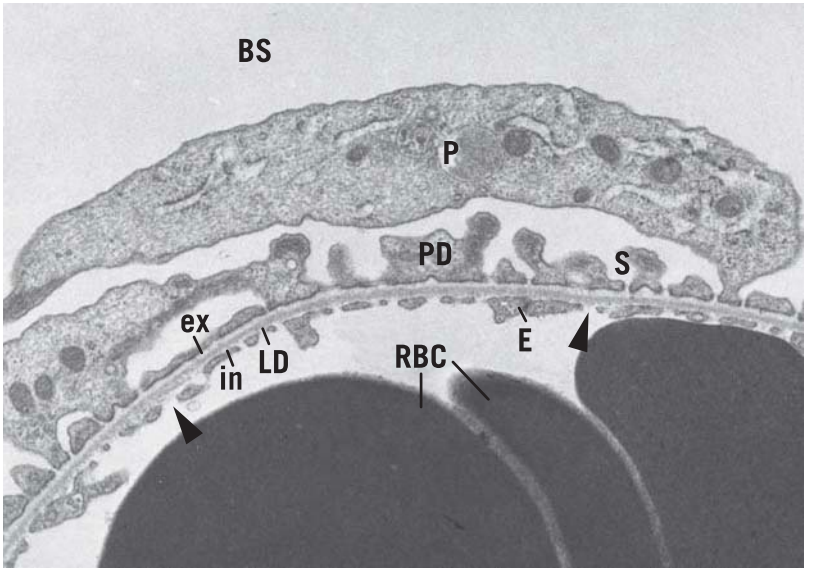


FIGURE 16.3. An electron micrograph of the renal filtration barrier. The primary process of a podocyte (P) in Bowman space (BS) gives off secondary processes, called pedicels (PD), which form a layer along the basal lamina enveloping the glomerular capillary. Between adjacent pedicels are the filtration slits (S) bridged by barely visible dense thin lines representing filtration slit membranes. The basal lamina consists of the lamina densa (LD), which is the major filtration barrier, and the laminae rara interna (in) and lamina rara externa (ex). Note the fenestrations (*arrowheads*) within the endothelial cells (E) lining the capillary, where red blood cells (RBC) are present (×14,000).

(2) The **lamina densa** contains **type IV collagen** (composed of α_3, α_4, and α_5 chains rather than the α_1 and α_2 chains present in most other lamina densa), **perlecan**, **laminin**, **entactin**, and **agrin**. The negative charges of some of these macromolecules and the filtration slit diaphragm act as a **selective macromolecular filter**, preventing passage of large protein molecules (molecular weight greater than 69,000 Daltons) into the Bowman space.

e. Glomerular filtration is the process whereby fluid from the blood exits the glomerular capillary bed and, as it passes through the filtration barrier, becomes the ultrafiltrate. In a healthy individual, approximately 1,250 mL of blood passes through the glomerular capillaries of the two kidneys every minute. Of this blood volume, 125 mL of fluid, known as the ultrafiltrate, enters the Bowman spaces (urinary spaces) of all the glomeruli of the two kidneys per minute. This process is known as the **glomerular filtration rate** (**GFR**) and is used to determine the functioning health of the kidneys. The GFR is corrected for the surface area of the body, so that a normal, adult, young male will have a GFR of 100 to 130 mL/min/1.73 m^2, whereas a young female will have a GFR of 90 to 110 mL/min/1.73 m^2. The GFR decreases as a function of age by 6 to 8 mL/min/decade, and as long as it remains greater than 60 mL/min/1.73 m^2, the kidneys are considered to be healthy.

CLINICAL CONSIDERATIONS

Glomerulonephritis, a type of nephritis characterized by **inflammation of the glomeruli**, is sometimes marked by proliferation of podocytes, endothelial cells, and mesangial cells in the glomerular tuft; infiltration of leukocytes is also common. This disease often occurs **secondary to a streptococcal infection** elsewhere in the body, which is thought to result in deposition of immune complexes in the glomerular basal lamina. The immune complexes damage the glomerular basal lamina and markedly reduce its filtering ability.

It is associated with production of urine-containing blood (**hematuria**), protein (**proteinuria**), or both; in severe cases, decreased urine output (**oliguria**) is common. It occurs in acute, subacute, and chronic forms. The chronic form, in which the destruction of glomeruli continues, leads eventually to renal failure and death.

Chronic renal failure can result from a variety of diseases (e.g., diabetes mellitus, hypertension, atherosclerosis) in which blood flow to the kidneys is reduced, causing a decrease in glomerular filtration and tubular ischemia. It is associated with pathologic changes (hyalinization) in the glomeruli and atrophy of the tubules, which impair virtually all aspects of renal function. It is marked by **acidosis** and **hyperkalemia** because the acid–base balance cannot be maintained, and by **uremia** because of the inability to eliminate metabolic wastes. If untreated, chronic renal failure leads to neurologic problems, coma, and death.

Alport syndrome is due to a mutation in the gene for the a5 chain of the type IV collagen, resulting in defective basal lamina formation in the kidney glomerulus (as well as in other regions of the body such as the eye and inner ear). Because the mutation is X-linked, males are more seriously affected than females, whose second X chromosome may not bear the same mutation. The effects on the kidney result in thickening of the basal lamina and the inability of the glomerular filtration to occur normally, so that protein and blood begin to appear in the urine. Eventually, in many patients, the result is kidney failure, and dialysis is required to sustain life. In certain patients, kidney transplant is not viable because the transplanted kidney's normal type IV collagen may be perceived as antigenic by the host, and the new kidney may be rejected by the immune system.

Rhabdomyolysis is a serious condition because of traumatic injury to skeletal muscles, such as from a heavy weight falling on and crushing a limb, strenuous exercise in hot weather, or damage from strenuous long distance running, which results in death of muscle fibers; however, other conditions, such as sickle cell anemia and even viral infections, third-degree burn, insect or snake venom, electrical shock, and certain medications such as high dosage of statins, may cause sufficient skeletal muscle damage causing rhabdomyolysis. The symptoms of this condition are very painful, weak muscles; problems running or even walking; discolored reddish brown to brown urine; tachycardia or irregular heartbeat; fever; vomiting; dehydration; abdominal discomfort; and even a state of confusion. Many, but not all patients will exhibit high levels of myoglobin, which is released from damaged muscles, in their urinalysis and blood test results as well as high levels of creatine kinase in their blood test results. Myoglobin becomes concentrated in the nephrons and forms casts that occlude the nephrons, thus debilitating urinary flow and damaging the kidney. Fortunately, rhabdomyolysis is reversible if treatment is initiated early after the muscle injury, but it may be lethal if it is untreated sufficiently early.

3. **Proximal convoluted tubule** (Figs. 16.4 to 16.6)
   a. **Structure**. The proximal convoluted tubule is lined by a single layer of **irregularly shaped** (cuboidal to columnar) epithelial cells that have microvilli forming a prominent **brush border**. These cells exhibit the following structures:
      (1) Apical canaliculi, vesicles, and vacuoles (endocytic complex) function in **protein absorption**.
      (2) Prominent interdigitations along their lateral borders interlock adjacent cells with one another.
      (3) Numerous **mitochondria** compartmentalized in the basal region by extensive infoldings of the basal plasma membrane supply energy for the **active transport of** Na^+ out of the tubule.
      (4) Apically situated occluding junctions block the paracellular pathway. And, the apical cell membrane has **glucose transporters**, **Na^+K^+- adenosine triphosphatase (ATPase) pump**, and an apically positioned tubulovesicular system designed to endocytose small proteins and peptides that escaped into the ultrafiltrate.
      (5) The basolateral cell membrane possesses a **Na^+-K^+ ATPase pump**, and, additionally, the basal cell membrane has glucose and amino acid transporters.
      (6) Each cell also possesses a primary cilium that functions in monitoring the flow and composition of the ultrafiltrate.
   b. **Function**
      (1) The proximal convoluted tubule drains the Bowman space at the urinary pole of the renal corpuscle.
      (2) It **resorbs** from the glomerular filtrate all of the glucose, amino acids, and small proteins and 60% to 80% of the sodium chloride and water and returns it into the peritubular capillary system to be distributed from there into the remainder of the body.
      (3) It **exchanges** H^+ in the interstitium for HCO_3^- in the filtrate.
      (4) It **secretes** organic acids (e.g., creatinine) and bases and certain foreign substances into the ultrafiltrate.
4. **Loops of Henle** (see Fig. 16.6)
   a. The **descending thick limb of the Henle loop**, also known as the straight portion (**pars recta**) of the proximal tubule, is lined by a simple **cuboidal** epithelium that has a prominent **brush border** and is similar to that lining the proximal convoluted tubule. It functions to resorb, exchange, and secrete in a manner similar to that of the proximal convoluted tubule.

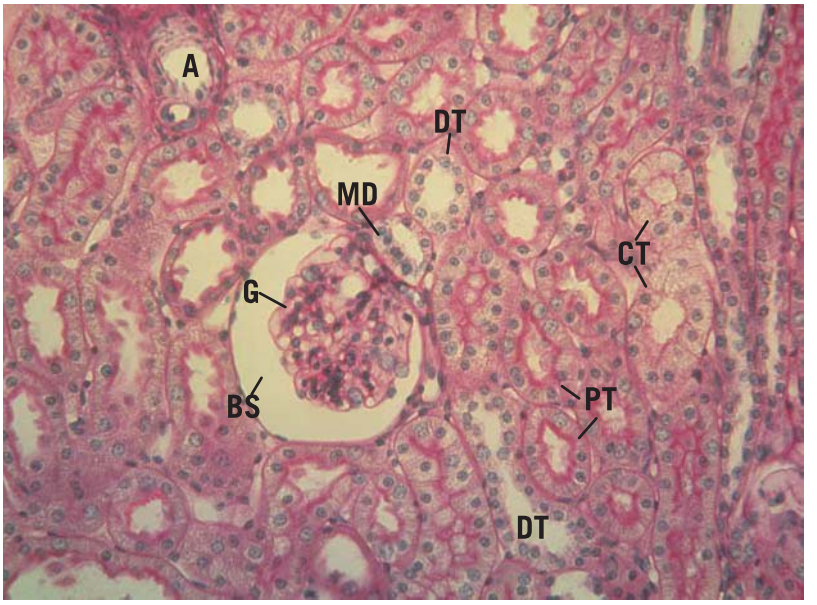


FIGURE 16.4. A light micrograph of components in the cortex of the kidney. A renal corpuscle showing the Bowman space (BS) and a glomerulus (G); the macula densa (MD) of a juxtaglomerular apparatus; many proximal tubules (PT) with prominent brush borders, and a few distal tubules (DT) and collecting tubules (CT), as well as an artery (A) are illustrated (×150).

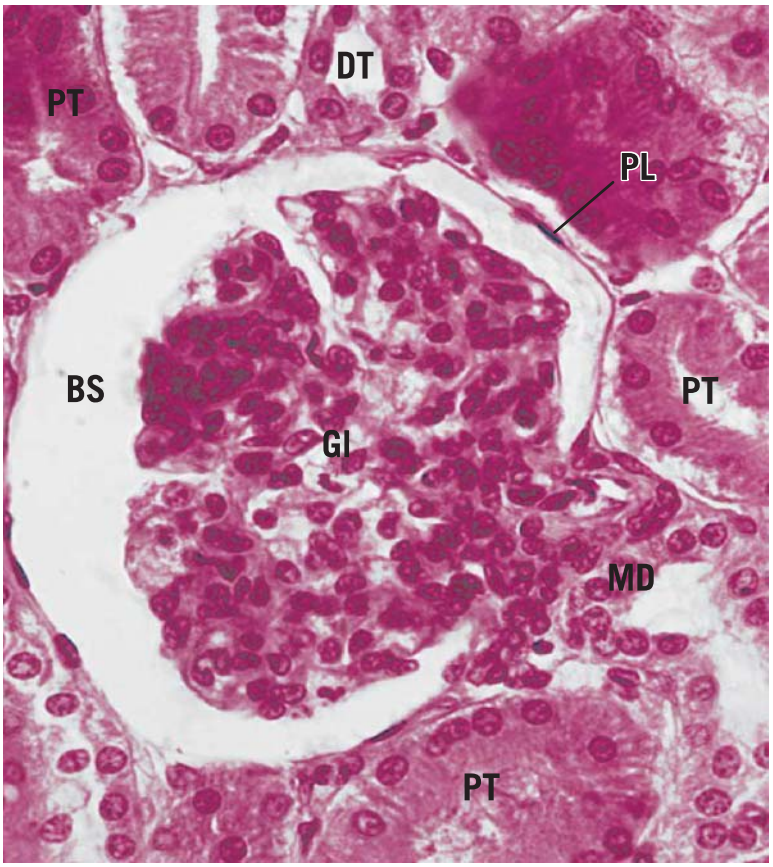


FIGURE 16.5. This is a higher magnification of a renal corpuscle similar to the one in Figure 16.4. Note that the parietal layer (PL) of the renal corpuscle is clearly visible, outlining the extent of the Bowman space (BS). The glomerulus (GI), a capillary bed, projects into the Bowman space and is invested by podocytes. Several profiles of the proximal convoluted tubule (PT) and distal convoluted tubule (DT) are labeled. One of the distal tubules displays its macula densa (MD) as it contacts an afferent (or efferent) glomerular arteriole (×540).

b. The **thin limb of the Henle loop** (see Fig. 16.6) is composed of a descending segment, a loop, and an ascending segment, all of which are lined by simple **squamous** epithelial cells possessing a few short microvilli. The nuclei of these cells bulge into the lumen. In ***cortical nephrons***, the thin limb is short and is composed of squamous epithelial cells that present neither interdigitations nor processes of their lateral membranes. In ***juxtamedullary nephrons***, the thin limb can be divided into **three** distinct portions on the basis of the three different types of simple squamous epithelial cells that form it: their organelle content, the depth of their tight junctions, and their permeability to water.

(1) Cells of the **descending thin limb** possess many aquaporin (AQP) 1 channels; therefore, this segment is very permeable to water as well as being somewhat permeable to ions such as sodium and chloride.

(2) The **Henle loop** itself is similar to the ascending thin limb and is mostly impermeable to water.

(3) The **ascending thin limb** is almost completely impermeable to water but possesses many sodium and chloride channels, which permit these ions to enter the cell from the lumen of the tubule and exit the cell into the renal interstitium. Additionally, urea enters the lumen of the ascending thin limb.

c. The **ascending thick limb of the Henle loop**, also known as the straight portion (**pars recta**) of the distal tubule, is lined by **cuboidal** epithelial cells that possess only a few microvilli, an apical nucleus, and mitochondria compartmentalized within basal plasma membrane infoldings. These cells manufacture and release a glycoprotein known as **uromodulin** (Tamm–Horsfall

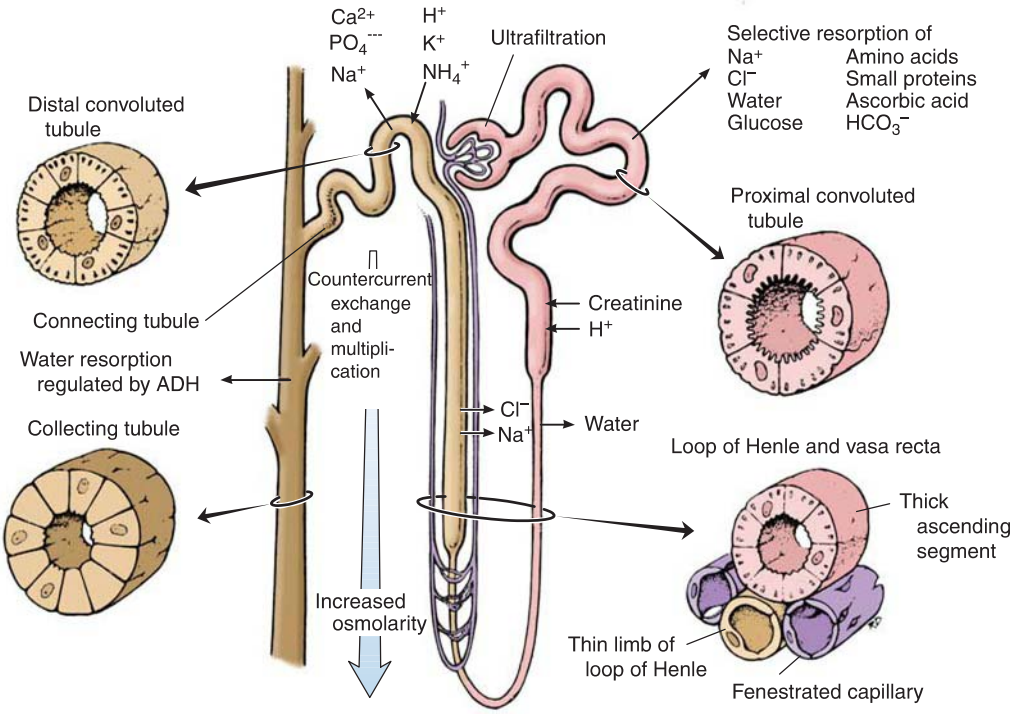


FIGURE 16.6 A uriniferous tubule showing its major structural and functional features and its vascular associations. ADH, antidiuretic hormone. (Adapted with permission from Williams PL, Warwick R, eds. *Gray's Anatomy*. 36th British ed. London: Churchill Livingstone; 1980:1393.)

glycoprotein) that reduces the ability of the kidney to form kidney stones and in some fashion reduces the possibility of urinary tract infections. Moreover, uromodulin also modulates the mechanism of urine concentration.

(1) It establishes a gradient of osmolarity in the medulla (see section 4.c.(1)).

(2) The ascending thick limb returns to the renal corpuscle of origin, where it is in close association with the afferent and efferent glomerular arterioles. In this region, the wall of the tubule is modified, forming the **macula densa**, which is part of the **juxtaglomerular (JG) apparatus**.

5. The **juxtaglomerular (JG) apparatus** is located at the **vascular pole** of the renal corpuscle. It is composed of the following:

a. JG cells are modified smooth muscle cells that exhibit some characteristics of protein-secreting cells, which are located primarily in the wall of the **afferent arteriole**, but a few may also be present in the efferent arteriole. They synthesize **renin** (a proteolytic enzyme) and store it in secretory granules.

b. Macula densa cells (see Figs. 16.4 and 16.5) are tall, narrow, closely packed epithelial cells of the **distal tubule**. They have elongated, closely packed nuclei that appear as a dense spot (macula densa) by light microscopy. These cells may **monitor the osmolarity and volume** of the fluid in the distal tubule and transmit this information to JG cells via the gap junctions between the two cell types. When the sodium concentration or the volume of the ultrafiltrate is reduced, the macula densa cells direct the JG cells to release their renin.

c. Extraglomerular mesangial cells, also known as **polkissen** (pole cushion) or **lacis cells**, lie between the afferent and efferent glomerular arterioles, but their functions are not understood.

d. The JG apparatus **maintains blood pressure** by the following mechanism:

(1) A **decrease in extracellular fluid volume** (perhaps detected by the macula densa as decreased ultrafiltrate volume), a **decrease in blood pressure** at the afferent glomerular arteriole, or a **decrease in sodium concentration** of the ultrafiltrate stimulates JG cells to release **renin** into the bloodstream.

(2) Renin acts on angiotensinogen (a large protein manufactured by hepatocytes of the liver) in the plasma. Renin cleaves the first 10 amino acids from angiotensinogen, converting it to **angiotensin I**. In capillaries of the lung and elsewhere, angiotensin-converting enzyme cleaves two amino acids from angiotensin I, converting it to **angiotensin II**, a potent vasoconstrictor that also stimulates release of **aldosterone** in the adrenal cortex and the **release of antidiuretic hormone (ADH)** by the neurohypophysis.

(3) Aldosterone stimulates the epithelial cells of the distal convoluted tubule to remove Na^+ and Cl^-. **Water follows the ions**, thereby **increasing the fluid volume** in the extracellular compartment, which leads to an increase in blood pressure.

(4) ADH causes the epithelial cells (mainly the **principal cells**) of the collecting tubule to add **AQP-2 channels** (as well as AQP-3 and AQP-4 channels) to their cell **membrane** and thus become permeable to water, releasing H_2O into the renal interstitium. As with the aldosterone mechanism discussed earlier, the increased extracellular fluid volume leads to elevation of the blood pressure.

6. The **distal convoluted tubule** (Fig. 16.7) is continuous with the macula densa and is similar histologically to the ascending thick limb of the Henle loop. It is much shorter and has a wider lumen than the proximal convoluted tubule and **lacks a brush border**. The distal convoluted tubule **resorbs Na^+** from the filtrate and actively transports it into the renal interstitium; this process is stimulated by **aldosterone**. It also transfers K^+, NH_4^+, and H^+ into the filtrate from the interstitium.
7. The **connecting tubule** is a short segment between the distal convoluted tubule and the collecting tubule into which it drains. It is lined by the following two types of epithelial cells:
   a. **Principal cells** have many infoldings of the basal plasma membrane. These cells **remove Na^+** from the filtrate and **secrete K^+** into it.
   b. **Intercalated cells** have many apical vesicles and mitochondria. These cells **remove K^+** from the filtrate and **secrete H^+** into it.

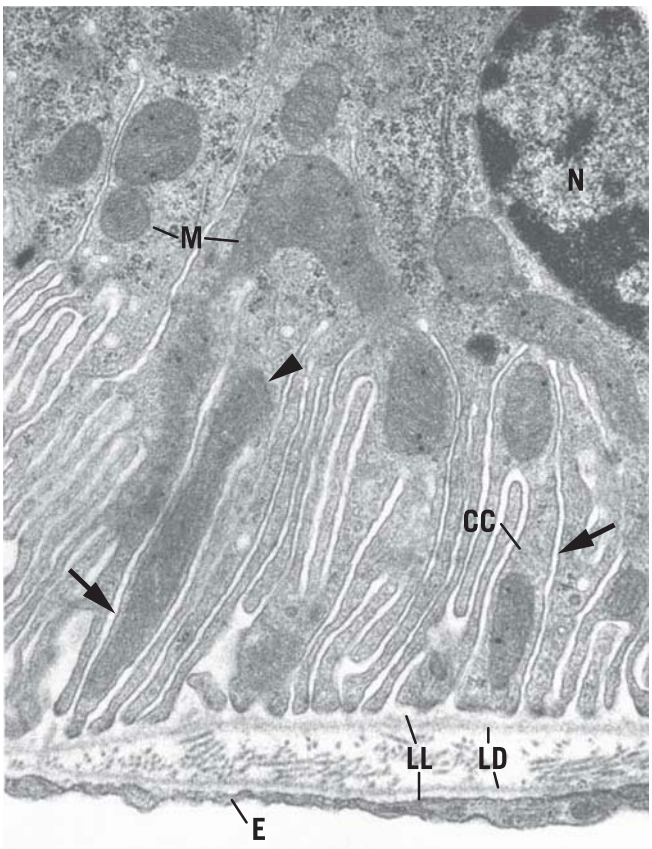


FIGURE 16.7. An electron micrograph of a cell in the distal convoluted tubule of the kidney. Elongated mitochondria (M) are located (*arrowhead*) within cytoplasmic compartments (CC) formed by deep infoldings of the basal plasma membrane where enzymes associated with ion transport are located. In between these extensive infoldings is extracellular space (*arrows*). These cells resorb Na^+ from the filtrate and actively transport it into the renal interstitium (aldosterone stimulates this process) and also transfer K^+, NH_4^+, and H^+ into the filtrate from the interstitium. Note the lamina densa (LD) and lamina lucida (LL), which form the basal lamina, the endothelial cell (E) lining a fenestrated capillary, and the apical nucleus (N) (×6,000).

CLINICAL CONSIDERATIONS

Nephrotoxic acute tubular necrosis is the death of kidney tubule cells caused by their exposure to a toxic drug or molecule, rather than a lack of oxygen (**ischemic** acute tubular necrosis). When a person suffers a crush injury causing significant muscle trauma, myoglobin is released from the muscle and enters the bloodstream. The myoglobin is filtered through the glomeruli, but it is toxic to cells of the kidney tubules, causing nephrotoxic acute tubular necrosis. If the damage is not too severe, the kidney tubule cells may be able to replace themselves, but, in severe cases, they cannot and the kidney may not completely recover.

B. **Collecting tubules (see Fig. 16.6) have a different embryonic origin from that of nephrons.** They have segments in both the cortex and medulla and converge to form larger and larger tubules.
   1. **Cortical collecting tubules** are located primarily within medullary rays, although a few are interspersed among the convoluted tubules in the cortex (**cortical labyrinth**). They are lined by a simple epithelium containing two types of **cuboidal** cells.
      a. **Principal (light) cells** possess a round central nucleus and a single **primary cilium**. These cells are responsible for the ability of the collecting tubules to concentrate urine because they possess AQP-2 channels, the principal ADH-regulated AQP channels, stored in their cytoplasm.
      b. **Intercalated (dark) cells** are less numerous than principal cells and possess microplicae (folds) on their apical surface and numerous apical cytoplasmic vesicles. The two types of intercalated cells are **α-intercalated cells** that have the ability to release **H^+ ions** into the tubular lumen, thus acidifying urine, and **β-intercalated cells** that have the ability to release **HCO^-_3 ions** into the tubular lumen, thus causing the urine to be more alkaline. α-Intercalated cells possess **hydrogen pumps**, and β-intercalated cells possess **HCO^-_3 pumps** to fulfill their function.
   2. **Medullary collecting tubules.** In the **outer** medulla, medullary collecting tubules are similar in structure to cortical collecting tubules and contain both **principal** and **intercalated cells** in their lining epithelium. In the inner medulla, the collecting tubules are lined only by **principal cells** (Fig. 16.8).

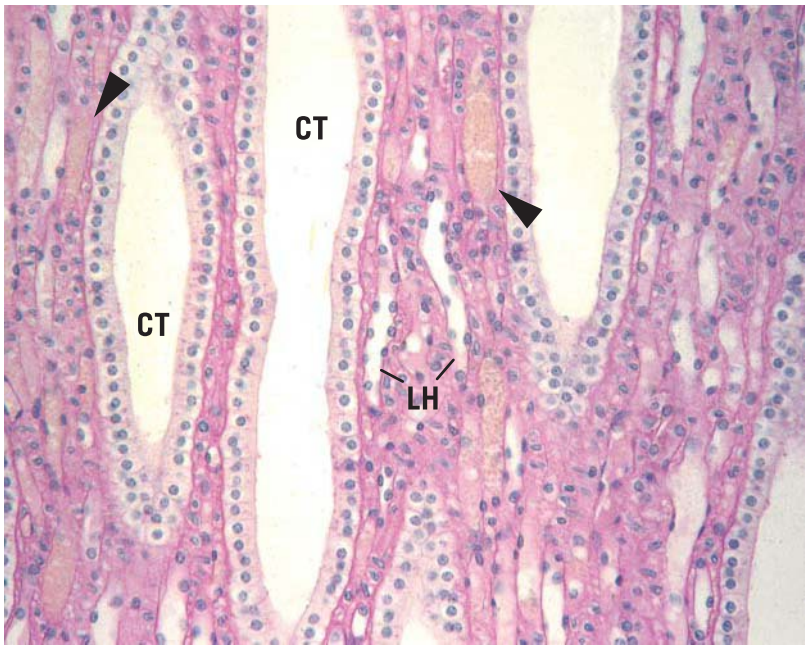


FIGURE 16.8. A light micrograph of components in the medulla of the kidney. Collecting tubules (CT) are lined by a simple columnar epithelium composed of cells displaying distinct lateral surfaces. The thin limbs of the loops of Henle (LH) are lined by a simple squamous epithelium whose cell nuclei bulge into the lumen, and capillaries (*arrowheads*) may be identified by the numerous red blood cells filling their lumens (×150).

3. **Papillary collecting tubules (ducts of Bellini)**, large collecting tubules (200–300 μm in diameter) formed from converging smaller tubules, are lined by a simple epithelium composed of **columnar** cells that have a single **primary cilium**. They empty at the **area cribrosa**, a region at the apex of each renal pyramid that has 10 to 25 openings through which the urine exits into a minor calyx.

IV. RENAL BLOOD CIRCULATION

The renal blood circulation is extensive, with total blood flow through both kidneys of about 1,200 mL/min. At this rate, all of the circulating blood in the body passes through the kidneys every 4 to 5 minutes.

A. Arterial supply to the kidney (Fig. 16.9)

1. **Branches of the renal artery** enter each kidney at the hilum and give rise to **interlobar arteries** that travel between the renal pyramids and divide into several **arcuate arteries**, which run along the corticomedullary junction parallel to the kidney's surface.
2. **Interlobular arteries**, smaller vessels that arise from the arcuate arteries, enter the cortical tissue and travel outward **between adjacent medullary rays**. They send branches to the interstitium just deep to the renal capsule. Adjacent interlobular arteries delimit a renal lobule.

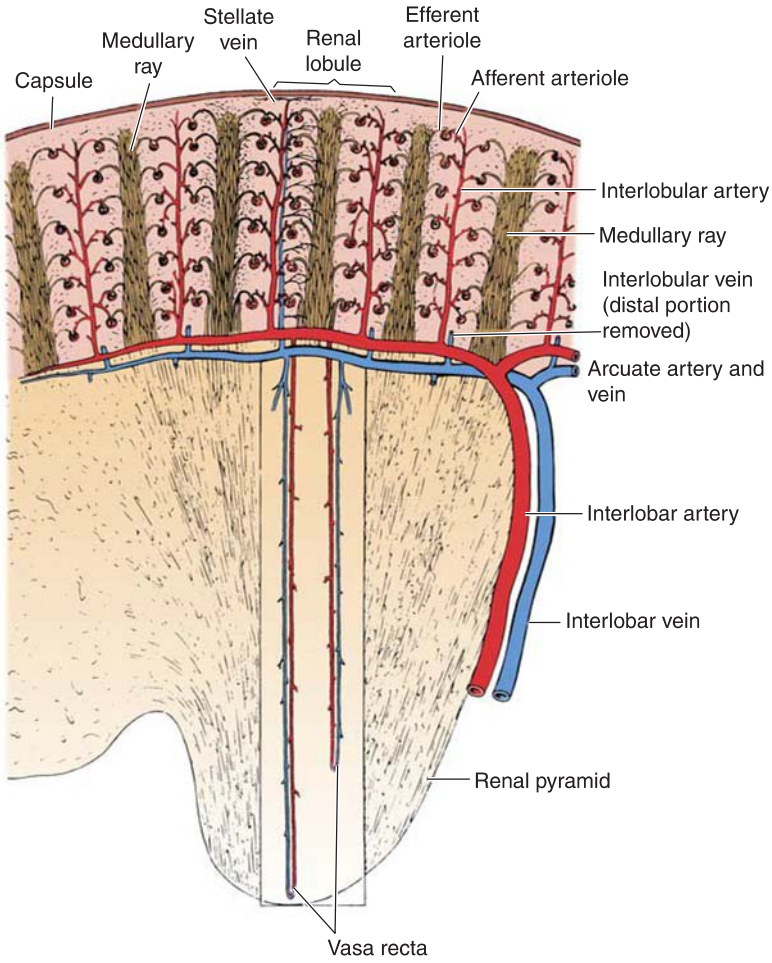


FIGURE 16.9. Blood circulation in the kidney. Arteries are shown in red and veins in blue. Adjacent interlobular arteries, which extend outward from the arcuate artery, define the boundaries of a renal lobule. (Reprinted with permission from Junqueira LC, Carneiro J, Kelley RO. *Basic Histology.* 9th ed. Stamford, CT: Appleton & Lange; 1998:375.)

3. **Afferent (glomerular) arterioles** are branches of the interlobular arteries that **supply the glomerular capillaries**.
4. **Efferent (glomerular) arterioles** arise from the glomerular capillaries and are associated with cortical, midcortical, and JG nephrons. They leave the glomerulus of cortical and midcortical nephrons and give rise to an extensive **peritubular capillary network** that supplies the cortical labyrinth, whereas those that leave the JG nephrons give rise to the **vasa recta**.
5. **Vasa recta** arise from the efferent glomerular arterioles of **juxtamedullary nephrons**.
   a. These long, thin vessels (**arteriolae rectae**) follow a straight path into the medulla and renal papilla, where they form capillaries and then loop back and increase in diameter toward the corticomedullary boundary (**venulae rectae**).
   b. They are closely **associated with the descending and ascending limbs of Henle's loops** and **collecting ducts**, to which they supply nutrients and oxygen.
   c. These vessels play a critical role in countercurrent exchanges with the interstitium.

B. **Venous drainage of the kidney (see Fig. 16.9)**
1. **Stellate veins** are formed by convergence of **superficial cortical veins**, which drain the outermost layers of the cortex.
2. **Deep cortical veins** drain the deeper regions of the cortex.
3. **Interlobular veins** receive both stellate and deep cortical veins and join **arcuate veins**, which empty into **interlobar veins**. These then converge to form a branch of the **renal vein**, which exits the kidney at the hilum.

V. REGULATION OF URINE CONCENTRATION

A. **Overview.** The regulation of urine concentration results in the excretion of large amounts of dilute (**hypotonic**) urine when water intake is high (**diuresis**) and of concentrated (**hypertonic**) urine when body water needs to be conserved (**antidiuresis**). This regulation depends on events that occur in the loops of Henle, vasa recta, and collecting tubules. It is affected by the presence or absence of **ADH**, which is secreted from the pars nervosa of the pituitary gland (neurohypophysis) when water must be conserved.

B. **The countercurrent multiplier system (Fig. 16.10) refers to the establishment of an *increasing osmotic concentration gradient* in the renal interstitium that extends from the outer medulla to the renal papilla.** It is produced by **ion and water exchanges** between the **filtrate in different parts of the loop of Henle** and the **renal interstitium:**
1. **In the descending limb of the loop of Henle**, the **isotonic** ultrafiltrate coming from the proximal convoluted tubules loses water to the interstitium and gains Na^+ and Cl^-, and the filtrate becomes **hypertonic**.
2. **In the ascending thin and thick limbs of the loop of Henle**, no water is lost from the ultrafiltrate because this part of the nephron is **impermeable to water** whether or not ADH is present.
   a. Cl^- is **actively transported** from the ultrafiltrate (in the ascending thick limb but **passively** in the ascending thin limb) into the interstitium, and Na^+ follows. In that fashion, an **osmotic gradient** is established in the **interstitium** of the outer medulla and the ultrafiltrate becomes **hypotonic**.
3. **In the distal convoluted tubule**, active resorption of Na^+ from the ultrafiltrate may occur in response to aldosterone, resulting in some water loss as well.

C. **Role of collecting tubules**
1. In the **absence of ADH**, the collecting tubules are **impermeable to water**. Thus, the hypotonic ultrafiltrate coming from the ascending limb of the loop of Henle is not changed, and **hypotonic urine** is excreted.
2. In the **presence of ADH**, the collecting tubules add AQP-2 channels (as well as AQP-3 and AQP-4 channels) into the cell membranes of their **principal cells** and thus become **permeable to water**. Thus, the isotonic ultrafiltrate entering the collecting tubules from the distal convoluted tubules loses water, and **hypertonic** (concentrated) **urine** is produced.

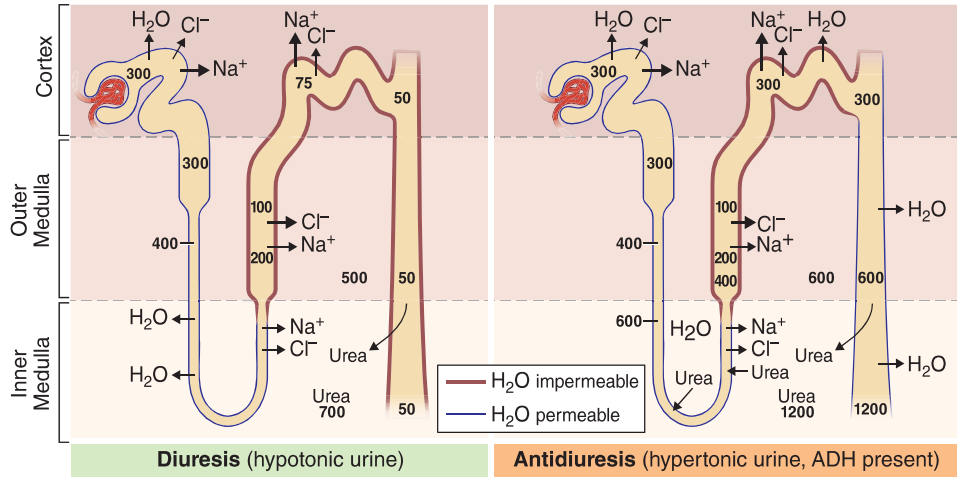


FIGURE 16.10. Summary of ion and water exchanges that occur in the uriniferous tubule in the absence (*left*) and presence (*right*) of antidiuretic hormone. The countercurrent multiplier system involving the loop of Henle produces an osmotic gradient in the medullary interstitium. Numbers refer to the local concentration in milliosmoles per liter. Segments of the tubule freely permeable to water are drawn with a thin line; impermeable segments are drawn with a thick line. In the distal convoluted tubule, some water follows sodium into the interstitium; sodium transport here is regulated by aldosterone. Note that the pars recta of the distal tubules actually contact their own renal corpuscles but they have been rotated in this diagram to facilitate easier identification.

CLINICAL CONSIDERATIONS

Diabetes insipidus results from destruction of the supraoptic and paraventricular nuclei in the hypothalamus, which synthesize ADH (vasopressin) (see Fig. 11.1). Diabetes insipidus is associated with a **decreased ability of the kidney to concentrate urine** in the collecting tubules because levels of ADH are reduced. Signs and symptoms include dehydration, excessive thirst (**polydipsia**), and excretion of **high volumes of dilute urine.**

For a discussion of **type 1, type 2, type 3, and monogenic diabetes**, see Chapter 15

D. **Countercurrent exchange system (Fig. 16.11) involves passive ion and water exchanges between the renal interstitium and the blood in the vasa recta, the small straight vessels associated with the loops of Henle.** This exchange system acts to maintain the interstitial osmotic gradient created by changes taking place in the Henle loop.

E. **The effect of urea (see Fig. 16.10) is to aid in the production and maintenance of the interstitial osmotic gradient, mostly in the inner medulla.**

1. **Urea** from the renal interstitium enters the uriniferous tubules at the loop of Henle, the ascending thin and thick limbs of the Henle loop, and the collecting tubules of the outer medulla.
2. **Urea concentrations** in the ultrafiltrate progressively increase as water is lost from the medullary collecting tubules, causing the urea to diffuse (passively) out into the interstitium and contributing to interstitial osmolarity.
3. A high-protein diet increases urea levels in the ultrafiltrate and its entrapment in the interstitium, thus enhancing the kidney's ability to concentrate the urine.
4. The ability of the kidney to concentrate urine depends mostly on the concentration of **sodium and chloride** in the renal interstitium of the **outer medulla**, but in the **inner medulla**, it is based mainly on the **urea** concentration in the renal interstitium.

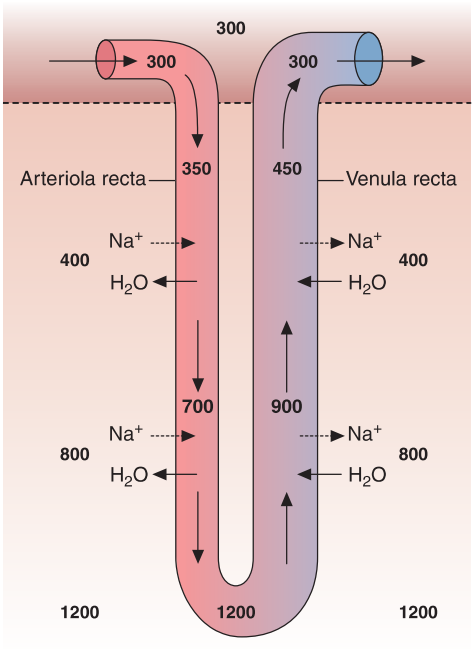


FIGURE 16.11. Countercurrent exchange mechanism. Summary of water and ion exchanges between the medullary interstitium and blood in the vasa recta. These countercurrent exchanges are *passive* and do not disturb the osmotic gradient in the interstitial tissue. Numbers refer to the local osmolarity per liter. (Adapted with permission from Junqueira LC, Carneiro J, Kelley RO. *Basic Histology*. 7th ed. Norwalk, CT: Appleton & Lange; 1992:390.)

table 16.2 Features of Excretory Passages

Region	Epithelium	Lamina Propria	Muscularis	Comments
Calyces, minor, major	Transitional epithelium	Reticular, elastic fibers	A few inner longitudinal and outer circular smooth muscle fibers	Urine from collecting tubules (ducts of Bellini) empty into minor calyces
Renal pelvis	Transitional epithelium	Reticular, elastic fibers	Inner longitudinal, outer circular layer of smooth muscle	Expanded upper portion of ureter receives urine from the major calyces
Ureters	Transitional epithelium lines stellate lumen	Collagen, elastic fibers	Inner longitudinal, outer circular layer of smooth muscle; lower third has additional outermost longitudinal layer	Peristaltic waves propel urine, so it enters bladder in spurts
Urinary bladder	Transitional epithelium: 5 or 6 cell layers in empty bladder; 3 or 4 cell layers in distended bladder. Trigone: triangular region; apices are openings of ureters and urethra	Fibroelastic connective tissue rich in blood vessels	Three poorly defined layers of smooth muscle; inner longitudinal, middle circular, outer longitudinal	Plasmalemma of dome- shaped cells in epithelium has unique plaques, elliptical vesicles underlying remarkable (empty vs. full) transition. Trigone, unlike most of bladder mucosa, always presents smooth surface
Urethra female	Transitional epithelium near bladder; remainder stratified squamous	Fibroelastic vascular connective tissue; mucus-secreting glands of Littre	Inner longitudinal, outer circular layer of smooth muscle; skeletal muscle sphincter surrounds urethra at urogenital diaphragm	Female urethra is conduit for urine. External sphincter of skeletal muscle permits voluntary control of micturition
Urethra male prostatic	Transitional epithelium near bladder; pseudostratified or stratified columnar	Fibromuscular stroma of prostate gland; a few glands of Littre	Inner longitudinal, outer circular layer of smooth muscle	Conduit for urine and semen. Receives secretions from prostate glands, paired ejaculatory ducts
Urethra male membranous	Pseudostratified or stratified columnar	Fibroelastic stroma; a few glands of Littre	Striated muscle fibers of urogenital diaphragm form external sphincter	Conduit for urine and semen. External sphincter of skeletal muscle permits voluntary control of micturition
Urethra male cavernous	Pseudostratified or stratified columnar; at fossa navicularis stratified squamous	Replaced by erectile tissue of corpus spongiosum; many glands of Littre	Replaced by sparse smooth muscle, many elastic fibers in septa lining vascular spaces in erectile tissue	Conduit for urine and semen. Receives secretions of bulbourethral glands present in urogenital diaphragm

VI. EXCRETORY PASSAGES

A. Overview (Table 16.2)

1. The excretory passages include the minor and major **calyces** and the **renal pelvis**, located within each kidney, and the **ureters**, **urinary bladder**, and **urethra**, located outside the kidneys.
2. These structures generally possess a three-layer wall composed of a **mucosa lined with transitional epithelium** (except in the urethra) lying on the lamina propria of connective tissue, a **muscularis (smooth muscle)**, and an **adventitia**.

B. The ureter conveys urine from the renal pelvis of each kidney to the urinary bladder.

It has a **transitional epithelium** that is thicker and contains more cell layers than that of the renal calyces. It possesses a **two-layer muscularis** (an inner longitudinal and outer circular layer of smooth muscle) in its upper two-thirds. The lowest third possesses an additional outer longitudinal layer of smooth muscle. The layers of the ureter contract to produce **peristaltic waves** that propel the urine so that it enters the bladder in spurts.

C. The urinary bladder (Fig. 16.12) possesses a *transitional epithelium* with a morphology that differs in the relaxed (empty) and distended (full) states, a thin lamina propria of *fibroelastic* connective tissue, and a *three-layer muscularis*.

1. The **epithelium of the relaxed bladder** is five to six cell layers thick and has **rounded dome-shaped cells** that bulge into the lumen. These cells contain unique **plaques** (having a highly ordered substructure) in their thick luminal plasma membrane and flattened **elliptical vesicles** in their cytoplasm.
2. The **epithelium of the distended bladder** is only three to four cell layers thick. Thus, the epithelium is thinner and has a larger luminal surface than that of the relaxed bladder; this results from insertion of the elliptical vesicles into the luminal plasma membrane of the surface cells. Its superficial cell layers are composed of **squamous cells**.

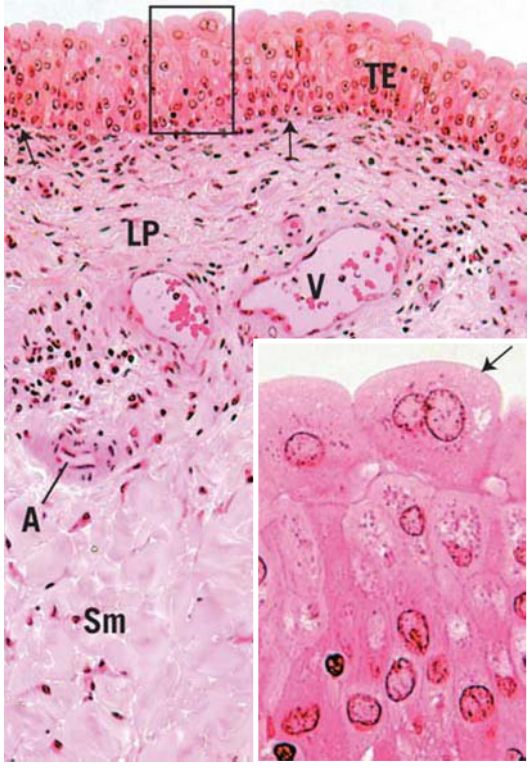


FIGURE 16.12. A light micrograph of the urinary bladder in a relaxed (empty) state. It is lined by transitional epithelium (TE) with dome-shaped surface cells and is separated from the underlying connective tissue by a basal lamina (*arrows*). A lamina propria (LP) of cellular, loose connective tissue may be distinguished from the submucosa (Sm) of dense connective tissue possessing many large collagen fibers. Note the venules (V) and an arteriole (A) present in the LP (×132). *Inset.* The *boxed region* of TE is here shown at higher magnification to demonstrate the large, dome-shaped surface cells (*arrow*), one of which is binucleated (×540). The TE undergoes marked changes. In contrast to the relaxed state of the bladder shown here, when the bladder is distended and full of urine, the dome-shaped surface cells become squamous because of the insertion of unusual "elliptical-shaped vesicles" into their plasma membrane, and the entire epithelium is often reduced to only three cell layers in thickness.

CLINICAL CONSIDERATIONS

Bladder cancer is two to three times more common in men than in women. More than 90% of bladder cancers originate in the transitional epithelium lining the organ. The most common sign of bladder cancer is blood in the urine (hematuria), which may not be visible to the naked eye. Frequent urination and/or pain during urination is sometimes present, but often the disease is symptomless. **Cystoscopy** is used to examine the lining of the bladder, to take tissue samples in order to characterize the tumor, and to determine the extent to which it has penetrated into the bladder wall. Superficial bladder cancer (limited to the epithelial layer) has a 5-year survival rate of about 85%, but invasive bladder cancer has a less favorable prognosis.

D. Urethra

1. The urethra conveys urine from the bladder to outside the body. In males, the urethra also carries semen during ejaculation. It has a **two-layer muscularis** consisting of an inner longitudinal and an outer circular layer of smooth muscle. At some point, the urethra is surrounded by an **external sphincter of skeletal muscle**, which permits its voluntary closure.
2. The **male urethra** is about 20 cm long and is divided into **prostatic**, **membranous**, and **cavernous** portions. It is lined by **transitional epithelium** in the beginning of the prostatic portion and by **pseudostratified** or **stratified columnar epithelium** in remainder and the other two portions. The **fossa navicularis**, located at the distal end of the cavernous urethra, is lined by **stratified squamous epithelium**. It houses mucus-secreting **glands of Littre** in the lamina propria.
3. The **female urethra** is much shorter (4–5 cm long) than the male urethra. It is lined primarily by **stratified squamous epithelium**, although patches of pseudostratified columnar epithelium are present. The female urethra may house **glands of Littre** in the lamina propria.

Review Test

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or completions of the statement. Select the ONE lettered answer that is BEST in each case.

1. A 35-year-old woman had surgery to remove a cerebral tumor. A month after the procedure, she reports being excessively thirsty and drinking several liters of water per day. She also urinated so frequently that she avoided leaving the house. Laboratory tests indicate that her urine has very low specific gravity. What is the most likely diagnosis of this woman's condition?

(A) Acute renal failure
(B) Glomerulonephritis
(C) Chronic renal failure
(D) Diabetes insipidus
(E) Urinary incontinence

Questions 2 through 5 refer to the following scenario:

As the glomerular filtrate passes through the uriniferous tubule, ions and water are exchanged (actively or passively) with the renal interstitium, resulting in the filtrate being isotonic, hypotonic, or hypertonic relative to blood plasma.

2. During a condition of antidiuresis, which part of the uriniferous tubule would contain a hypertonic filtrate?

(A) Ascending thick limb of the loop of Henle
(B) Bowman (capsular) space
(C) Cortical collecting tubule
(D) Medullary collecting tubule
(E) Proximal convoluted tubule

3. During a condition of antidiuresis, which part of the uriniferous tubule would contain an isotonic filtrate?

(A) Ascending thick limb of the loop of Henle
(B) Bottom of descending thin limb of loop of Henle
(C) Bowman (capsular) space
(D) Medullary collecting tubule
(E) Papillary collecting tubule

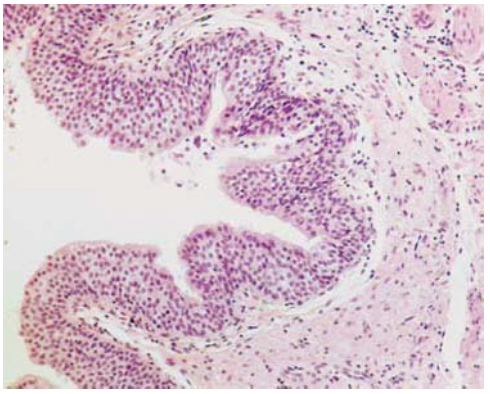
4. During a condition of antidiuresis, which one of the following parts of the uriniferous tubule would contain a hypotonic filtrate?

(A) Bowman (capsular) space
(B) Cortical collecting tubule
(C) Distal portion of the ascending thick limb of the loop of Henle
(D) Medullary collecting tubule
(E) Proximal convoluted tubule

5. During a condition of antidiuresis, which part of the uriniferous tubule would contain a hypertonic filtrate?

(A) Bottom of descending thin limb of loop of Henle
(B) Bowman (capsular) space
(C) Distal portion of the ascending thick limb of the loop of Henle
(D) Pars recta of the proximal tubule
(E) Proximal convoluted tubule

Question 6 refers to the photomicrograph below:



6. The patient who had surgery to remove this structure was suffering from

(A) glomerulonephritis.
(B) bladder cancer.
(C) aortic stenosis.
(D) renal arterial stenosis.
(E) portal hypertension.

7. What is the underlying cause of Alport syndrome?

(A) Glomerulonephritis
(B) Streptococcal infection
(C) Type IV collagen defect
(D) Hypertension
(E) Increased low-density lipoprotein blood levels.

8. Which of the following structures is present in the male urethra but is not present in the female urethra?

(A) Stratified squamous epithelium
(B) Pseudostratified columnar
(C) Glands of Littre
(D) External sphincter of skeletal muscle
(E) Connective tissue layer underlying the epithelium

9. The countercurrent multiplier system in the kidney involves the exchange of water and ions between the renal interstitium and

(A) blood in the vasa recta.
(B) blood in the peritubular capillary network.
(C) filtrate in the proximal convoluted tubule.
(D) filtrate in the loop of Henle.
(E) filtrate in the medullary collecting tubule.

10. What is the most common agent causing glomerulonephritis?

(A) Herpes virus
(B) Streptococci
(C) *Neisseria*
(D) *Clostridium*
(E) Human immunodeficiency virus

Answers and Explanations

1. **D.** This woman has diabetes insipidus. Surgical removal of the cerebral tumor likely damaged her hypothalamus, which, in turn, greatly reduced or eliminated the production of ADH. Therefore, her kidney collecting tubules and distal tubules fail to resorb water, resulting in the production of vast quantities of dilute urine and causing excessive thirst.
2. **D.** The filtrate that enters the cortical collecting tubules is nearly isotonic. When ADH is present (antidiuresis), water is removed from the filtrate in the collecting tubules, making the filtrate hypertonic by the time it reaches the medullary collecting tubules.
3. **C.** Filtration of blood in the renal corpuscle yields an isotonic ultrafiltrate that enters the Bowman (capsular) space.
4. **C.** The ascending thick limb of the loop of Henle is impermeable to water even in the presence of ADH, but it actively transports Cl^- from the filtrate into the interstitium (Na^+ follows passively). As a result, the filtrate becomes hypotonic as it approaches the distal convoluted tubule.
5. **A.** The filtrate remains isotonic from the Bowman space throughout the proximal tubule, including the pars recta (also called the thick descending limb of the loop of Henle). As it passes through the descending thin limb of the loop of Henle, the filtrate loses water to the interstitium and gains Na^+ and Cl^-, becoming hypertonic.
6. **B.** The photomicrograph is taken from the urinary bladder and the patient was suffering from bladder cancer.
7. **C.** Alport syndrome is due to a mutation in the gene for the α5 chain of the type IV collagen resulting in defective basal lamina formation in the kidney glomerulus. Because the mutation is X-linked, males are more seriously affected than females, whose second X chromosome may not bear the same mutation.
8. **B.** Only the male urethra contains pseudostratified columnar epithelium. Stratified squamous epithelium lines most of the female urethra and the distal end of the cavernous urethra in males. Mucus-secreting glands of Littre are always present in the male urethra and may be present in the female urethra.
9. **D.** The countercurrent multiplier system in the loop of Henle involves ion and water exchanges between the filtrate and the interstitium. It establishes an osmotic gradient in the interstitium of the medulla, which is greatest at the papilla.
10. **B.** Glomerulonephritis, a type of nephritis characterized by inflammation of the glomeruli, is sometimes marked by proliferation of podocytes, endothelial cells, and mesangial cells in the glomerular tuft; infiltration of leukocytes is also common. This disease often occurs secondary to a streptococcal infection elsewhere in the body, which is thought to result in deposition of immune complexes in the glomerular basal lamina. The immune complexes damage the glomerular basal lamina and markedly reduce its filtering ability.

chapter 17

Female Reproductive System

I. OVERVIEW—FEMALE REPRODUCTIVE SYSTEM

A. The female reproductive system consists of the paired *ovaries* and *oviducts*; the *uterus, vagina,* and *external genitalia*; and the paired *mammary glands*, although, technically, the mammary glands are part of the integument because they are highly modified sweat glands. It undergoes marked changes at the onset of puberty, which is initiated by **menarche**, and exhibits monthly menstrual cycles and menses from puberty until the end of the reproductive years, which terminate at **menopause**.

II. OVARIES (Figs. 17.1 and 17.2)

A. Overview and embryonic development. The ovaries are covered by a simple cuboidal epithelium called the **germinal epithelium**, deep to which is the capsule of the ovary, known as the **tunica albuginea** that is composed of a dense, irregular collagenous connective tissue. Each ovary is subdivided into a **cortex** and a **medulla**, which are not sharply delineated.

1. Development

a. Around the third week of development, a ridge of tissue forms, on both sides of the embryo, between the lateral and paraxial mesoderms, known as the intermediate mesoderm, which becomes the **urogenital ridge**. Part of the urogenital ridge gives rise to the nephrogenic ridge, responsible for the development of the urinary system, and, during the fifth week of embryogenesis, part of it gives rise to the **gonadal ridge**, which will develop into the genital system. During the sixth week of embryogenesis, **primitive germ cells** leave the **yolk sac** to enter the gonadal ridges. Once there, they undergo cell division and increase their number. The gonadal ridges do not as yet have distinguishing male or female characteristics and, therefore, they are referred to as **indifferent gonads**.

b. Approximately 6 weeks later (during the fourth month of development), each primitive germ cell, now referred to as an oogonium, is surrounded by the single layer of flattened cells known as follicular cells, which invaginated and migrated from the germinal epithelium. Only about 500,000 oogonia will be surrounded by follicular cells; oogonia that have no follicular cell sheath are driven into **apoptosis**.

c. The oogonia that are surrounded by follicular cells begin their first meiotic division and are known as **primary oocytes.** In response to the meiotic division, the follicular cells manufacture and release a *meiosis-preventing factor* known as **oocyte maturation inhibitor (OMI)** that arrests the primary oocyte in the diplotene stage of the first meiotic division and the primary oocytes remain in that arrested development until they are ovulated (which could be 40 years later). The primary oocyte and its sheath of flat follicular cells, together, are known as the **primordial follicle**.

d. Between birth and the 11th year of life, more than 60% of the primordial follicles degenerate, and each ovary will be left with approximately 80,000 primordial follicles.

B. The ovarian cortex consists of ovarian follicles in various stages of development and a connective tissue *stroma*, which contains cells that respond in unique ways to hormonal stimuli.

1. Ovarian follicles (Table 17.1; also see Figs. 17.1 and 17.2)

a. Primordial follicles are the ovary's **basic reproductive units** and each one is composed of a **primary oocyte** enveloped by a single layer of flat **follicular cells** (see Fig. 17.2). All primordial follicles are in a state of **arrested development** until in some unknown fashion, but probably involving members of the **transforming growth factor β superfamily**, some **primordial follicles** are "**recruited**" (**activated**) to begin to form a group of growing follicles. There appears to be an interaction involving follicular cells, primary oocytes, and mesenchymal cells of the ovarian cortex and, possibly, **insulin** and **follicle-stimulating hormone** (**FSH**) may also have a role in the recruitment of primordial follicles.

(1) Primary oocytes display a prominent, acentric, vesicular-appearing nucleus (**germinal vesicle**) possessing a single nucleolus. They have many Golgi complexes, mitochondria, profiles of rough endoplasmic reticulum (RER), and well-developed annulate lamellae as well as **cortical granules** located just beneath the oocyte plasmalemma that contains enzymes that cleave proteins.

(a) As stated earlier, primary oocytes become **arrested in prophase** (**dictyate stage**) **of meiosis I** by paracrine factors (**OMI**) produced by the follicular cells of the embryo and remain in this stage until ovulation (perhaps for as long as 40 years).

(2) Follicular cells are attached to one another by **desmosomes** and are separated from the surrounding stroma by a basal lamina.

b. Growing follicles. The **granulosa cells** of all growing follicles secrete **anti-Müllerian hormone** (**Müllerian inhibiting substance**), a substance that inhibits primordial follicles from being recruited, thus limiting the number of growing follicles and maintaining a cadre of primordial follicles that may be recruited throughout the woman's reproductive period.

(1) Primordial and primary follicles are **not dependent on FSH** for their development; instead, local factors, such as **epidermal growth factor**, **insulin-like growth factor**, **activin**, and **Ca^{+2} ions**, stimulate the development of primordial and primary follicles. However, some authors are suggesting that even these early follicles may be FSH dependent.

(2) Primary follicles are of two types, unilaminar and multilaminar. They possess an amorphous layer, the **zona pellucida (ZP)**, produced by, and surrounding, the primary oocyte (although some authors suggest that the follicular cells also make a contribution to its formation). The ZP separates the follicular cells from the primary oocyte. Follicular cells of the primary follicles begin to express **FSH receptors** on the surface of their cell membranes and they also form gap junctions with each other as well as with the microvilli of the primary oocyte. A basal lamina is present at the interface of the follicular cells with the stroma.

(a) The ZP, the glycoprotein covering of the primary oocyte, is composed of four glycoproteins, known as ZP 1, ZP 2, ZP 3, and ZP 4. The function of ZP 4 is not known.

table 17.1 Stages in the Development of Ovarian Follicles

Stage	Zona Pellucida	Follicular Cell Layer (Granulosa)	Liquor Folliculi	Theca	Hormone Dependency
Primordial follicle	Not present	Single layer of flat cells	Not present	Not present	Dependent on local factors
Unilaminar primary follicle	Present	Single layer of cuboidal cells	Not present	Not present	Dependent on local factors
Multilaminar primary follicle	Present	Multiple layers of granulosa cells	Not present	Interna, externa present	Dependent on local factors
Secondary follicle	Present	Spaces among granulosa cells	Accumulates in spaces among granulosa cells	Interna, externa present	FSH dependent
Graafian follicle	Present	Forms membrana granulosa, cumulus oophorus	Fills the antrum	Interna, externa present	FSH dependent until becomes dominant follicle

FSH, follicle-stimulating hormone.

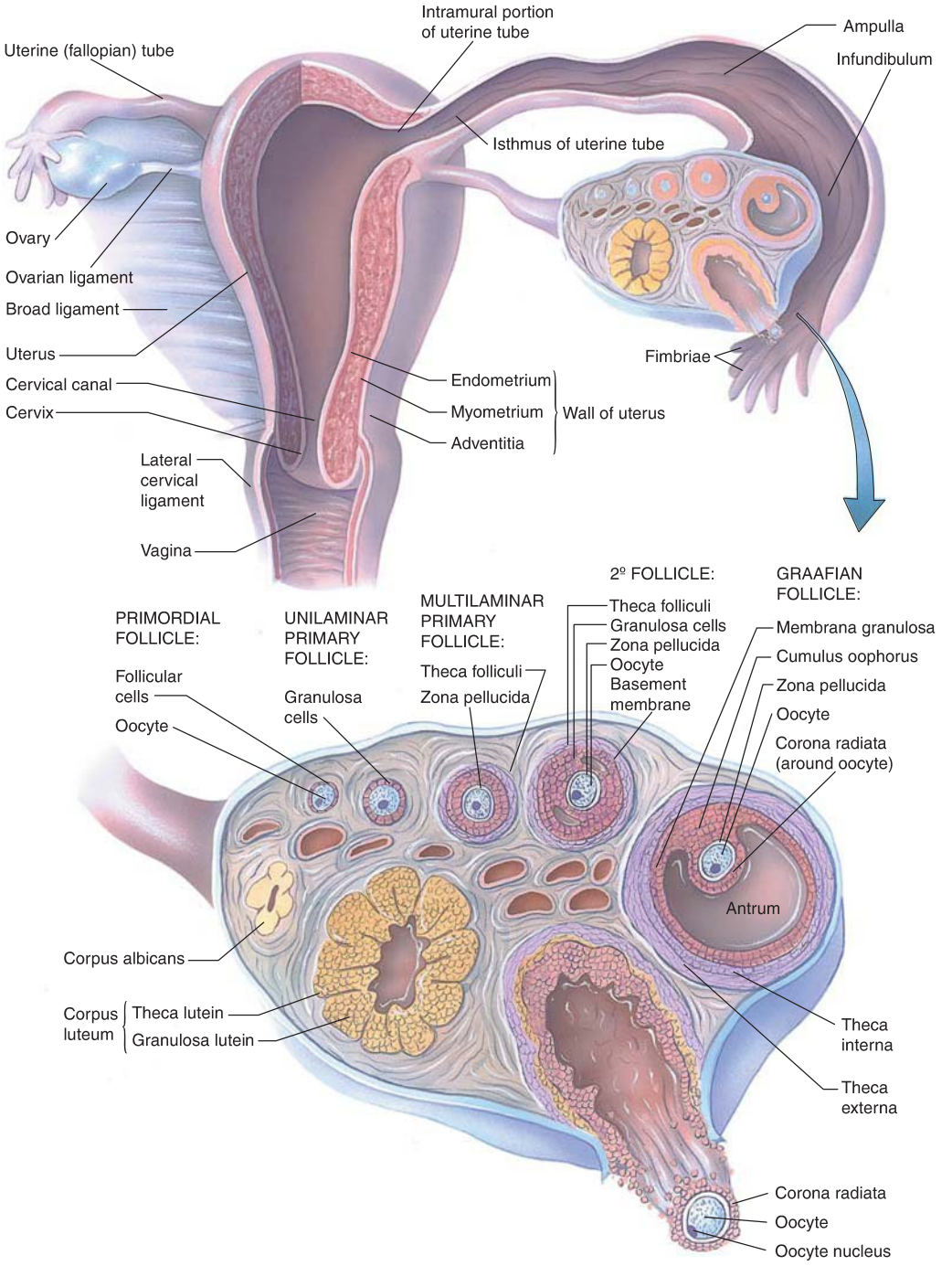


FIGURE 17.1. Structural features of the ovary. Follicles and corpus luteum are in different stages of development. Each follicle houses a *primary oocyte* arrested in the prophase of the first meiotic division. The most developed Graafian follicle releases its oocyte during ovulation. As that primary oocyte is being released, it finishes its first meiotic division, becomes a *secondary oocyte*, and is arrested in the *metaphase* stage of the second meiotic division. Subsequent to ovulation, the Graafian follicle differentiates into the *corpus luteum*, which will eventually degenerate into the *corpus albicans*. (Reprinted with permission from Gartner LP. *Color Atlas of Histology*. 7th ed. Baltimore, MD: Wolters Kluwer; 2018:382.)

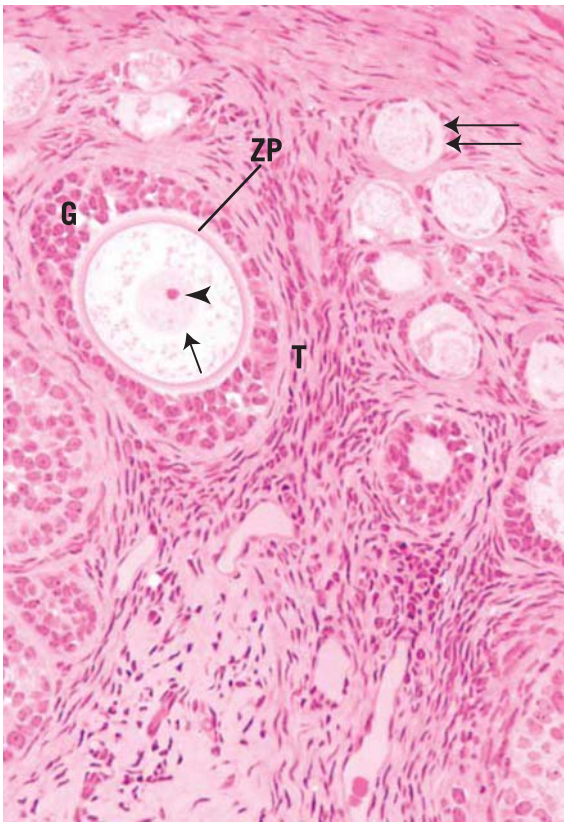


FIGURE 17.2. The cortex of this monkey ovary displays the presence of primordial follicles (*double arrows*) as well as several multilaminar primary follicles, one of whose constituent structures is labeled. Nucleus (*arrow*), nucleolus (*arrowhead*), zona pellucida (ZP), granulosa cells (G), and theca (T) (×270).

ZP 2 and **ZP 3** permit the binding of spermatozoon and facilitate the occurrence of the **acrosome reaction**.

(b) After fertilization (discussed below) has occurred, the ovum secretes the enzyme **ovastacin**, which degrades ZP 2, thereby preventing the binding of additional spermatozoa to the ZP. In order to ensure that only one spermatozoon can fertilize the ovum, **ZP 1** cross-links the remaining ZP 2 with ZP 3, thus preventing the binding of additional spermatozoa.

1. **Unilaminar primary follicles** develop from primordial follicles and are composed of a single layer of **cuboidal** follicular cells surrounding the primary oocyte.
2. **Multilaminar primary follicles** (see Fig. 17.2) develop from unilaminar follicles by proliferation of follicular cells. They proliferate because of the protein **activin**, a product of the primary oocyte. Activin also promotes both the release of FSH and its binding to FSH receptors. Additionally, the primary oocyte releases the growth factors **bone morphogenetic protein 15 (BMP-15)** and **growth differentiation factor 9 (GDF-9)**, both of which induce granulosa cell proliferation. These follicles consist of several layers of follicular cells; these follicular cells are now also known as **granulosa cells**.
   - **(1)** Multilaminar primary follicles are circumscribed by two layers of stromal cells: an inner cellular layer (**theca interna**) and an outer fibromuscular layer (**theca externa**). The theca interna is separated from the granulosa cells by a basal lamina.
   - **(2)** **Granulosa cells** secrete **stem cell factor** (**kit ligand**) that binds to kit ligand receptors on the surface of the **primary oocyte plasmalemma** as well as to kit ligand receptors on the surface of the **theca interna cell membranes**. The binding to **primary oocyte** kit ligand receptors is responsible for growth of the

primary oocyte, and binding to kit ligand receptors on the **theca interna cells** facilitates their organization around the developing follicles.

(3) Cells of the theca interna manufacture **androstenedione** (male sex hormone) and express **luteinizing hormone** (**LH**) **receptors** on their cell membranes. Androstenedione penetrates the basal lamina and enters the granulosa cells, where the enzyme **aromatase** converts the male hormone into **estrogen**, the female hormone.

CLINICAL CONSIDERATIONS

Mutations that affect the normal connexin synthesis result in the absence of Graafian follicle formation as well as the inability of the oocyte to undergo meiotic division, with consequential female infertility. The most probable cause of the defects is the inability to exchange various necessary factors between follicular cells to the primary oocyte via the faulty gap junctions.

Mutation in the AR gene (the gene on the X chromosome that codes for androgen receptors), an X-linked recessive disorder, occurs rarely, no more than 1 per 20,000 live births. Individuals who have this mutation are said to have **complete androgen insensitivity syndrome** if they have no functional androgen receptors. Genetically they are usually male, having an X and a Y chromosomal complement. They possess female *external genital* characteristics (including breasts after puberty), but usually lack both pubic hair and underarm hair, have no uterus, and are, therefore, infertile. However, they have undescended testes, which should be removed surgically because they may become cancerous later in life.

(3) **Secondary** (**antral**) **follicles** are established when a fluid, the **liquor folliculi**, an exudate of plasma containing various hormones, such as activin, estrogen, follistatin, inhibin, and progesterone, and OMI, begins to accumulate in the spaces between granulosa cells. The OMI, synthesized by the granulosa cells, prevents the oocyte from becoming larger than 125 μm in diameter and from completing its first meiotic division. The fluid-filled spaces will begin to coalesce, eventually to form a single large cavity called an antrum. Secondary follicles are **dependent on FSH**.

(a) Granulosa cells contact each other via gap junctions and also form gap junctions with the cell membrane of the primary oocyte (within the ZP).

(b) Just as in the normal development of the primary follicle, the conversion from primary to secondary follicles is greatly dependent on **BMP-15** and **GDF-9**.

(c) Both granulosa cells and theca interna cells express LH receptors on their plasma membranes; additionally, granulosa cells also express FSH receptors on their cell membranes.

c. Graafian (mature) follicle

(1) The dominant Graafian follicle, approximately 2.5 cm in diameter and evident as a large bulge on the surface of the ovary, is the one follicle among the secondary follicles that **will ovulate**. It is **FSH independent** and manufactures the hormone **inhibin** that shuts off FSH release by the basophils of the anterior pituitary gland, causing atresia of the other developing follicles (secondary and nondominant Graafian follicles).

(2) The primary oocyte is positioned off center on a small mound of granulosa cells (**cumulus oophorus**) that project into the hyaluronic acid–rich **liquor folliculi**–containing **antrum** of the follicle. Granulosa cells surround the ZP. Those contacting the ZP are known as the **corona radiata**. Other granulosa cells line the antrum, forming the **membrana granulosa**.

(3) Theca interna cells, in response to LH binding to their LH receptors, manufacture **androstenedione** (**androgen**), which is transferred to granulosa cells. The granulosa cells, under the influence of FSH binding to their FSH receptors, transform androstenedione into testosterone and, by the use of the enzyme **aromatase**, convert the testosterone into **estrogen** (estrogen is a generic term for substances that exert similar biologic effects to those of **17b-estradiol**).

(4) The **theca externa** is composed of collagenous connective tissue enriched with a plethora of smooth muscle cells. It is also richly supplied with many blood vessels, which provide nourishment to the theca interna.

(5) **Ovulation**

(a) An LH surge from the pituitary gland, along with the local factor manufactured by the primary oocyte, **maturation promoting factor** (a complex of **cycline-dependent kinase** and **cyclin B**), triggers the **primary oocyte** to complete its first meiotic division just prior to **ovulation**, forming a **secondary oocyte** and the **first polar body**. The second meiotic division is triggered by the presence of local meiosis-inducing factors, but its progress is blocked at metaphase.

(b) The same LH surge also triggers **ovulation**. The secondary oocyte and its **corona radiata** cells leave not only the ruptured follicle but also the ovary at the ovarian surface to enter the fimbriated end of the oviduct.

(c) The remnant of the Graafian follicle becomes the **corpus hemorrhagicum** that is transformed into the **corpus luteum of menstruation**, a temporary structure that may remain functional for a couple of weeks and then degenerates into the **corpus albicans**. If the woman is pregnant, the corpus hemorrhagicum becomes transformed into the **corpus luteum of pregnancy**, which remains functional for several months, and then it also degenerates into the **corpus albicans**.

(6) **Time period of folliculogenesis.** Although the prior description of folliculogenesis seems to suggest that the entire process occurs within a single menstrual cycle, that is not the case. In fact, once a primordial follicle is recruited for development, almost a year is required before ovulation can occur, and to go from primordial to a completely developed secondary follicle takes approximately 290 days and another 60 days or so for that follicle to become ovulated.

CLINICAL CONSIDERATIONS

Some women experience a sudden abdominal (or pelvic) pain in the middle of their menstrual cycle (**mittelschmerz**) that lasts 2 or 3 hours (although it may last as long as 48–72 hours or even longer), and they have attributed that to the process of ovulation. Although this attribution was not universally accepted, the sudden **surge of LH** is now known to be followed by a similar surge in **prostaglandin $F_{2\alpha}$**, a pharmacologic agent that causes sudden, cramp-like contractions of the ovarian, fallopian tube, or uterine smooth muscle fibers. This violent contraction is responsible for the pain experienced by some women. Other causes, such as painful distension of the ovarian follicles or the rupture of the tunica albuginea of the ovary, may also contribute to the ovulation pain.

2. The **corpus hemorrhagicum** is formed from the remnants of the Graafian follicle. After the oocyte, with its corona radiata, leaves the ovary a little blood enters and forms a clot in the former antrum and within a short period of time macrophages and connective tissue elements enter the region and the macrophages dispose of the blood clot and other cellular debris. Once the macrophages have performed their function, the corpus hemorrhagicum, under the influence of various hormones, is converted into the corpus luteum. The hormones responsible for this transformation are: estrogen, prolactin, LH, human chorionic gonadotropin (hCG), and insulin-like growth factors I and II.
3. The **corpus luteum**, composed of **granulosa lutein cells** (modified granulosa cells) and **theca lutein cells** (modified theca interna cells), is formed from the corpus hemorrhagicum. As the corpus hemorrhagicum collapses upon itself, its cellular components become greatly modified to form this LH-dependent richly vascularized **temporary endocrine gland**. The basement membrane between the theca interna and the former membrana granulosa disintegrates and blood and lymph vessels arising from the theca interna invade the former membrana granulosa.
   a. **Granulosa lutein cells**, derived from cells of the membrana granulosa, are large (30 μm in diameter), pale cells that possess an abundance of smooth endoplasmic reticulum, RER, many mitochondria, a well-developed Golgi complex, and lipid droplets. They manufacture **progesterone** and convert androgens formed by the theca lutein cells into **estrogen**.

b. **Theca lutein cells**, derived from cells of the theca interna, are small (15 μm in diameter) and are concentrated mainly along the periphery of the corpus luteum. They manufacture **progesterone** and **androgens** and small amounts of estrogen.

4. The **corpus albicans** is the remnant of the degenerated corpus luteum. Its formation is due to the hypoxic conditions present in the corpus luteum as fibroblasts manufacture an overabundance of collagen. The fibrotic event elicits the arrival of **T cells** that release **interferon-γ**, a chemoattractant for macrophages, which release **tumor necrosis factor** α, a cytokine that drives both granulosa lutein and theca lutein cells into apoptosis. As the cell death and fibrosis progress, the corpus albicans contracts and becomes a small scar on the surface of the ovary.
5. **Atretic follicles**, commonly present in the ovary, are follicles in various stages of maturation that undergo degeneration as evidenced by pyknotic changes in the nuclei of the granulosa cells and other degenerative changes. Degeneration of these follicles occurs because the **dominant follicle** that ovulated its secondary oocyte releases **inhibin** that shuts off FSH production by the basophils of the anterior pituitary gland.

C. **The ovarian medulla contains large blood vessels, lymphatic vessels, and nerve fibers in a loose connective tissue stroma.** They also possess a small number of **estrogen**-secreting **interstitial cells** and a few **androgen**-secreting **hilar cells**.

D. **Hormonal regulation (Figs. 17.3 and 17.4)**

1. **Control of follicle maturation and ovulation**
   a. The primary oocyte of unilaminar primary follicles secretes **activin**, which facilitates proliferation of granulosa cells. Granulosa cells secrete **stem cell factor** (**kit ligand**) that binds to kit ligand receptors on the surface of the **primary oocyte plasmalemma** as well as to kit ligand

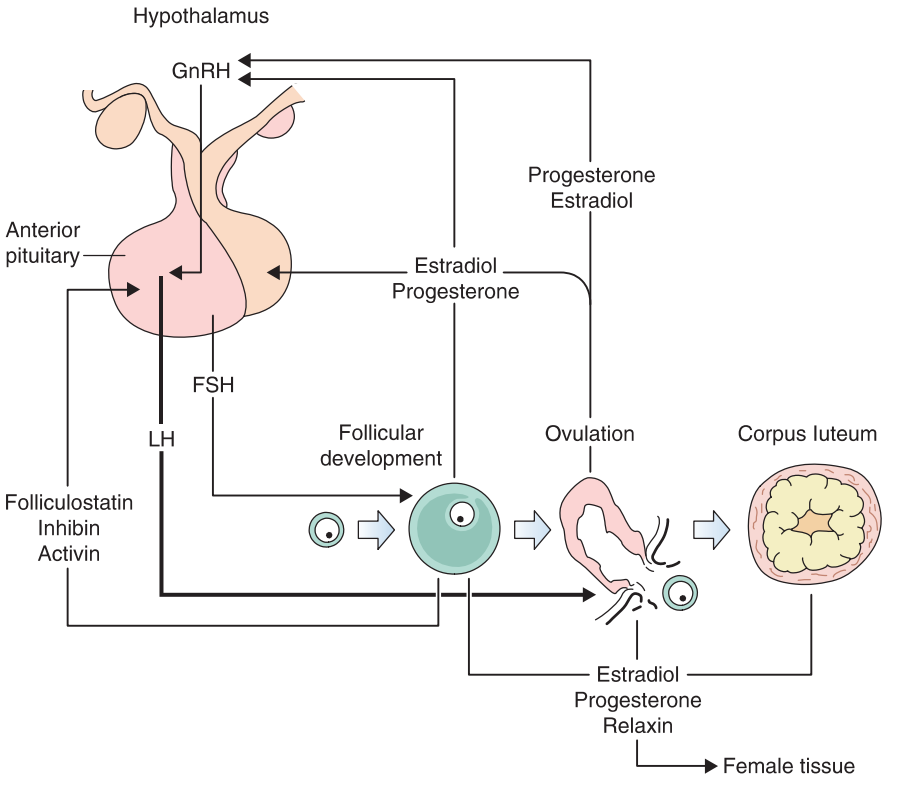


FIGURE 17.3. The hormonal relationship between the hypophysis and the reproductive system. The preferred term for gonadotropin-releasing hormone (GnRH) is luteinizing hormone–releasing hormone. FSH, follicle-stimulating hormone; LH, luteinizing hormone. (Adapted with permission from Gartner LP. *Textbook of Histology*. 4th ed. Philadelphia, PA: Elsevier; 2017:537.)

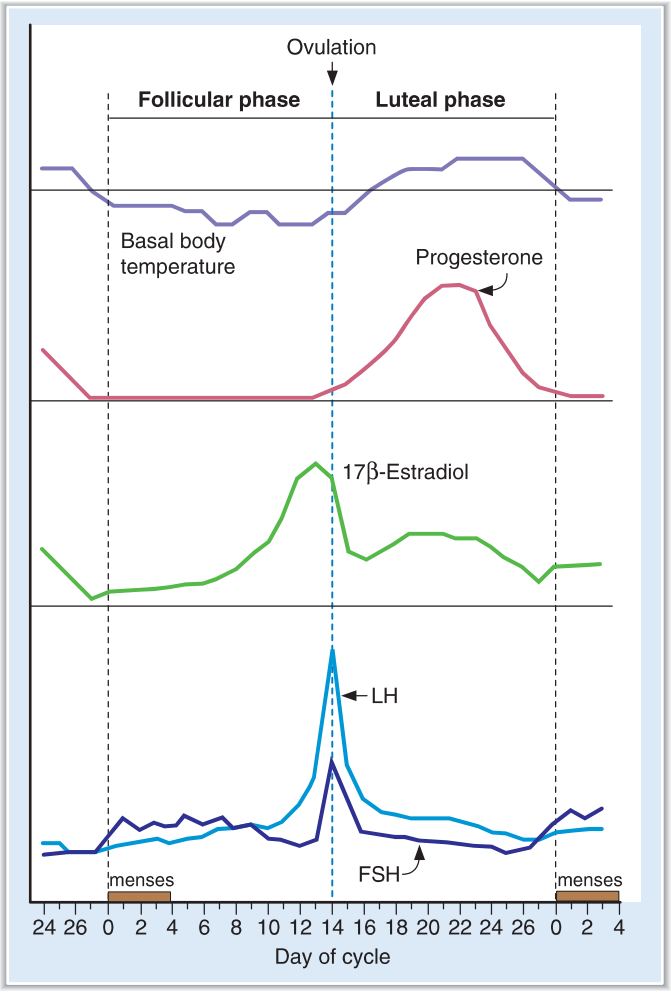


FIGURE 17.4. Hormonal response and basal body temperature at various stages of the menstrual cycle. Observe that before and at ovulation the basal body temperature and progesterone blood levels are beginning to increase from a low level; estradiol levels reached their highest point just before and continue decreasing. LH and FSH levels reach their highest levels at ovulation. FSH, follicle-stimulating hormone; LH, luteinizing hormone. (Reprinted with permission from Costanzo, L. *Board Review Series: Physiology*. 6th ed. Baltimore, MD: Wolters Kluwer; 2015.)

receptors on the surface of the **theca interna cell membranes**. The binding to **primary oocyte** kit ligand receptors is responsible for growth of the primary oocyte, and binding to kit ligand receptors on the **theca interna cells** facilitates their organization around the developing follicles.

b. Both the normal development of the primary follicle and the conversion from primary to secondary follicles are greatly dependent on **BMP-15** and **GDF-9** .

c. **Luteinizing hormone–releasing hormone** (**LHRH**) (also known as gonadotropin-releasing hormone) from the hypothalamus causes the release of FSH and LH from the pars distalis of the pituitary gland.

d. **FSH** stimulates the growth and development of secondary (but, according to most authors, not earlier stage) ovarian follicles and the appearance of LH receptors on the granulosa cell plasmalemma. The regulation of FSH and LH is influenced by the following:

(1) Theca interna cells manufacture androgens, which are converted to estrogen by granulosa cells. Granulosa cells also secrete inhibin, follistatin, and activin, all of which (in addition to estrogen) regulate FSH secretion.

(2) By approximately day 14 of the menstrual cycle, estrogen blood levels are sufficiently high to facilitate a sudden, brief surge of LH.

e. **Surge of LH**

(1) A surge of LH triggers the primary oocyte of the **dominant Graafian follicle** to complete meiosis I and to enter meiosis II, where it is arrested at metaphase; it initiates ovulation of the secondary oocyte from the Graafian follicle and formation of the corpus luteum.

(2) The dominant Graafian follicle is no longer FSH dependent, and it releases the hormone **inhibin** that shuts off FSH release by the anterior pituitary, causing **atresia** of all developing FSH-dependent follicles.

2. **Fate of the corpus luteum**
   a. **Progesterone**, the major hormone secreted by the corpus luteum, inhibits the release of LH by suppressing the release of LHRH but promotes development of the uterine endometrium. **Estrogen** inhibits the release of FSH by suppressing the release of LHRH, and **relaxin** facilitates parturition.
   b. **In the event of pregnancy**, the developing placenta manufactures hCG and human chorionic somatomammotropin (hCS).
      (1) **hCG**, manufactured by the syncytiotrophoblasts (and, to a certain extent, by cytotrophoblasts), maintains the corpus luteum of pregnancy for about 3 months, at which time the placenta takes over the production of progesterone, estrogen, and relaxin.
      (2) **hCS**, manufactured by the syncytiotrophoblasts, regulates glucose metabolism and stimulates mammary gland duct proliferation.
   c. **In the absence of pregnancy**, neither LH nor hCG is present, and the **corpus luteum begins to atrophy**; the lack of estrogen and progesterone also triggers the release of FSH from the pituitary, thus reinitiating the menstrual cycle.
3. In each menstrual cycle, only about five maturing follicles reach the Graafian follicle stage, and usually only the **dominant follicle** undergoes ovulation. As mentioned earlier, the dominant follicle is FSH independent; it produces a surge of **inhibin** that suppresses FSH production and leads to atrophy of the other maturing follicles.

CLINICAL CONSIDERATIONS

Polycystic ovarian syndrome (PCOS) is a rather common condition that may start soon after puberty or may start later during a woman's reproductive age, especially if the patient experienced significant increase in her weight. In order to be diagnosed with PCOS, two of three conditions must be present: increased blood androgen levels (with the possible accompaniment of hirsutism, masculinization, and acne), polycystic ovaries (as evidenced by ultrasound), and irregular menstrual cycles. The causes of PCOS are not known, but it has a familial component, and it may be caused by excess insulin levels (which result in increased androgen levels), leading to chronic low-grade inflammation. PCOS may cause various problems, such as miscarriage, infertility, type 2 diabetes, and even endometrial cancer. Treatment modalities include weight loss and treatment with birth control pills to decrease the ovarian production of androgens.

Luteinized unruptured follicle (LUF) syndrome is an uncommon syndrome in which the dominant follicle fails to ovulate its secondary oocyte. Fortunately, this condition does not usually lead to infertility, but it does reduce the probability of pregnancy. It may lead to endometriosis as there appears to be a statistical correlation between the two conditions. Because the syndrome frequently resolves itself, some have suggested that LUF syndrome may be stress related.

III. OVIDUCTS (FALLOPIAN TUBES OR UTERINE TUBES)

Each of the two **oviducts** is about 12 cm in length and is subdivided into four regions: the **infundibulum**, which has a **fimbriated end**; the **ampulla**, which is its longest region (about 7 cm in length) and is the most common site of fertilization; the **isthmus**; and the **intramural portion**, which traverses the wall of the uterus. The wall of each oviduct consists of a **mucosa**, **muscularis**, and **serosa**.

A. **The mucosa has extensive *longitudinal folds* in the infundibulum.** The degree of folding progressively decreases in the remaining three regions of the oviduct (Fig. 17.5).
   1. The **epithelium** is **simple columnar** and consists of peg cells and ciliated cells.
      a. **Peg cells** (see Fig. 17.5), whose cytoplasm contains abundant RER, a well-developed Golgi complex, and many apical electron-dense secretory granules, secrete a **nutrient-rich medium**

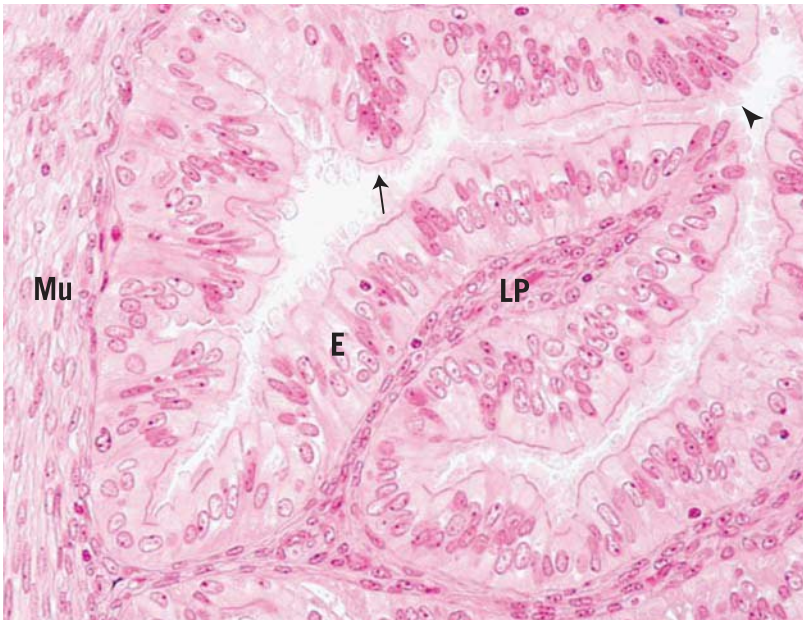


FIGURE 17.5. The mucosa of the ovary is highly convoluted, forming finger-like processes, whose epithelial lining (E) is composed of two cell types, ciliated columnar cells (*arrow*) and peg cells (*arrowhead*). The richly vascularized lamina propria (LP) and the surrounding smooth muscle (Mu) coat are clearly evident (×270).

that nourishes the spermatozoa (and preimplantation embryo) as well as cytokines that aid in the **capacitation** of spermatozoa. The presence of progesterone increases the number of peg cells.

b. **Ciliated cells** (see Fig. 17.5) possess many cilia, whose number and intensity of motion are increased by the presence of estrogen, beat mostly toward the lumen of the uterus. Ciliated cells aid in the transport of the developing embryo to the uterus.

2. The **lamina propria** (see Fig. 17.5) consists of loose connective tissue containing reticular fibers, fibroblasts, mast cells, and lymphoid cells.

B. **The muscularis (see Fig. 17.5), composed of an ill-defined inner circular and an outer longitudinal layer of smooth muscle, contract rhythmically to assist in moving the developing embryo toward the uterus.**

C. **The serosa, which is composed of a simple squamous epithelium overlying a thin connective tissue layer, covers the outer surface of the oviduct.**

CLINICAL CONSIDERATIONS

Tubal pregnancy constitutes almost 90% of all **ectopic pregnancies**, a condition where the developing embryo implants itself in the oviduct. This is a very dangerous condition because the slender oviduct cannot accommodate the growing embryo, whose increasing diameter places pressure on the wall of the oviduct, causing it to burst. This results in massive bleeding and possible death of the mother. Warning signs of tubal pregnancy occur in about 50% of the women, and these are pain in the abdominal region, which may radiate to the shoulder, and perhaps vaginal bleeding. The risk of tubal pregnancy increases with each previous incidence. Although the causes of tubal pregnancies are not known, women who smoke, women have had pelvic inflammatory disease or surgery of the oviduct, and women who are undergoing in vitro fertilization or are using fertility medications have been shown to have an increased chance of tubal pregnancies. Although the incidence of tubal pregnancy is less than 2 in 100 live births and is doubled in women receiving assisted reproductive techniques, 10% of deaths occurring during the first trimester are due to tubal pregnancies.

IV. UTERUS

The uterus has three regions: the **fundus**, **body** (**corpus**), and **cervix**.

A. The uterine wall consists of the *endometrium*, *myometrium*, and *adventitia* (or serosa).

1. The **endometrium** (Fig. 17.6), composed of an epithelial lining and a gland-rich connective tissue stroma, undergoes hormone-modulated cyclic alterations during the **menstrual cycle**, varying in thickness from less than 1 mm to as much as 7 mm. Its lumen is lined by a **simple columnar** epithelium containing **secretory** and **ciliated cells**. Its stroma resembles mesenchymal connective tissue, with **stellate cells** and an abundance of **reticular fibers**. Macrophages and leukocytes are also present. The stroma houses the **simple tubular glands** of the endometrium.
   a. The **endometrium** has two layers: functionalis and basalis.
      (1) The **functionalis** (**functional layer**) is the thick superficial layer of the endometrium that is sloughed and reestablished monthly as a result of hormonal changes during the menstrual cycle.
      (2) The **basalis** (**basal layer**) is the deeper layer of the endometrium that is about 1 mm or less in thickness and is preserved during menstruation. It has endometrial **glands**, whose basal cells provide a source for **reepithelialization** of the endometrium after the functional layer is shed.
   b. The **endometrial vascular supply** consists of two types of arteries derived from vessels in the **stratum vasculare** of the myometrium: **coiled arteries** extend into the functional layer and undergo pronounced changes during various stages of the menstrual cycle; **straight arteries** do not undergo cyclic changes and terminate in the basal layer.

CLINICAL CONSIDERATIONS

Endometriosis is a condition in which the pelvic peritoneal cavity contains uterine endometrial tissue. It is associated with hormone-induced changes in the ectopic endometrium during the menstrual cycle. As the endometrium is shed, bleeding occurs in the peritoneal cavity, causing severe pain and the formation of cysts and adhesions. It may lead to **sterility** because the ovaries and oviducts become deformed and embedded in scar tissue. The factors that contribute to the occurrence of endometriosis are not known.

Endometrial cancer, the most frequently occurring carcinoma of the female genital tract, occurs much more frequently in postmenopausal women than in women in their fourth and fifth decades of life and is exceptionally rare in women younger than 30 years. The most readily noted symptom of endometrial cancer is vaginal spotting in postmenopausal women (and between periods in younger women), pain in the pelvic region, enlargement of the uterus, and any unusual, watery/bloody vaginal discharge. Although what causes endometrial cancer is not known, certain predisposing factors have been identified, such as nonmenstrual uterine bleeding, diabetes, obesity, PCOS, having had no pregnancies, having family members with uterine cancer, age, and taking tamoxifen for breast cancer treatment. If endometrial cancer is suspected, digital pelvic examination, ultrasound, dilation and curettage, and hysteroscopy may all be employed to confirm the suspicion. The four stages of endometrial cancer depend on the extent of the lesion. Stage I is confined to the uterus; stage II involves the uterus and the cervix; stage III involves lymph nodes of the pelvic region but not the bladder and rectum; stage IV involves the rectum, bladder, and perhaps regions outside the confines of the pelvis. Treatment involves total hysterectomy (removal of the uterus and cervix) along with removal of the oviducts and ovaries. Additionally, many of the lymph nodes that receive lymph from the affected region may be excised. Following surgery, radiation, chemotherapy, and hormone therapy may be employed.

2. The **myometrium**, the thick smooth muscle tunic of the uterus, is composed of inner and outer longitudinal layers and a thick middle circular layer. The circular layer is richly **vascularized** and is often referred to as the **stratum vasculare**.
   a. The myometrium thickens during pregnancy because of the hypertrophy and hyperplasia of individual smooth muscle cells. Near the end of pregnancy, the myometrium develops many

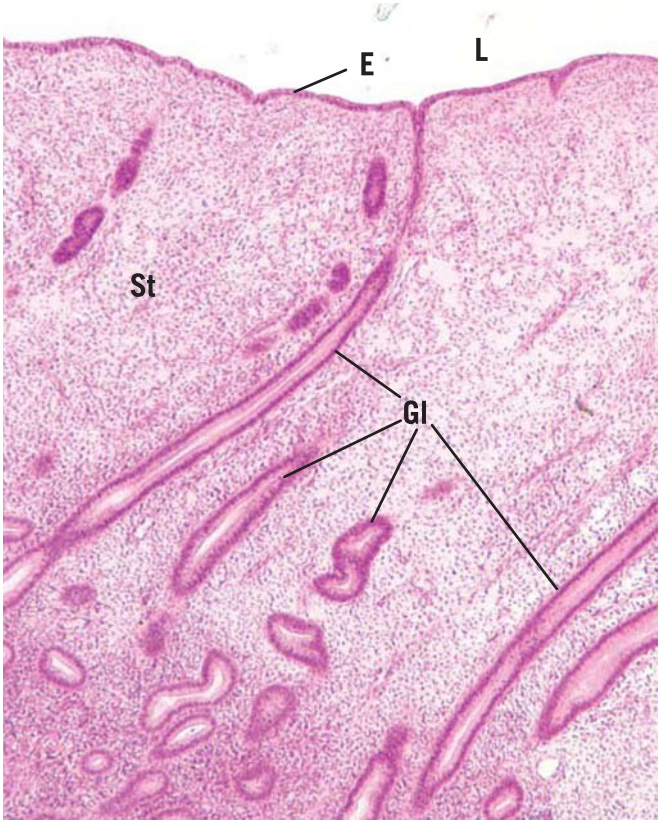


FIGURE 17.6. The uterine mucosa is in the process of being rebuilt during the follicular phase. The connective tissue stroma (St) is well developed, and uterine glands (Gl) are being formed and are beginning to become coiled. A simple columnar epithelium (E) lines the lumen (L) of the uterus (×53).

gap junctions between its smooth muscle cells. These junctions coordinate contraction of the muscle cells during parturition.

b. At parturition, the myometrium undergoes powerful contractions triggered by the hormone **oxytocin** and by **prostaglandins** (both of which are increased at term). After parturition, the myometrium shrinks because many of the smooth muscle cells become deprived of estrogen and, therefore, undergo **apoptosis**.

3. **External covering**
   - **a. Serosa** is present over surfaces of the uterus bulging into the peritoneal cavity.
   - **b. Adventitia** is present along the retroperitoneal surfaces of the uterus.

B. The menstrual cycle begins on the day menstrual *bleeding appears*. At this time, the blood levels of **estrogen**, **progesterone**, **FSH**, and **LH** are very low (see Fig. 17.4).

1. **Menstrual phase** (**days 1–4**) is characterized by a **hemorrhagic discharge** (**menses**) of the functional layer of the endometrium. It is triggered by **spasms of contraction** and **relaxation** of the coiled arteries (caused by low levels of progesterone and estrogen). Long-term (2–3 days) **vasoconstriction** of these arteries causes ischemia and eventual necrosis. During this phase of the menstrual cycle, blood clotting is inhibited.
   - **a.** Vasoconstriction is followed by sudden, intermittent **vasodilation** of the coiled arteries, which ruptures their walls, flooding the stroma with blood, detaching the functional layer, and dislodging the necrotic tissue.
   - **b.** Because the basal layer is supplied by short straight vessels that do not undergo prolonged vasoconstriction, it is not sloughed and does not become necrotic.
2. The **proliferative** (**follicular**) **phase** (see Fig. 17.6), **days 4 to 14**, follows the menstrual phase and involves **renewal of the entire functional layer**, including the repair of glands, connective tissue,

and vascular elements (specifically, the coiled arteries). During the proliferative phase, the level of **estrogen** in the blood continues to rise, and this is the principal hormone responsible for the stage of proliferation.

a. The epithelium that lines the luminal surface of the uterus is renewed by mitotic activity of cells remaining in uterine glands of the basal layer of the endometrium. During this phase, the glands are straight and lined by a simple columnar epithelium and the stromal cells divide, accumulate glycogen, and enlarge.

b. Coiled arteries extend approximately two-thirds of the way into the endometrium, which, at the end of the proliferative phase, is approximately 3 mm in thickness.

3. The **secretory** (**luteal**) **phase** (**days 15–28**) begins shortly after ovulation and is characterized by a **thickening of the endometrium**, resulting from edema and secretion by the endometrial glands. **Progesterone** and, to a certain degree, **estrogen** are the principal hormones driving the secretory phase.

a. Glands become **coiled**, their lumina become filled with a secretion of **glycoprotein material** and **glycogen**, and their cells accumulate large amounts of **glycogen** in the basal aspect of their cytoplasm.

b. Coiled arteries become not only more highly coiled but also longer, extending into the superficial aspects of the functional layer.

c. At the end of the secretory phase, the endometrium is somewhat edematous and is approximately 6 to 7 mm in thickness.

CLINICAL CONSIDERATIONS

Uterine prolapse is a condition in which the uterine ligaments, namely the round ligament, broad ligament, uterosacral ligaments, and the ligament of the ovary, are no longer able to maintain the normal anatomical position of this organ, and the uterus slides down and bulges into the vagina. The uterus may occupy only the upper one-third of the vagina or may slide all the way down to protrude through vaginal orifice between the labia minora. Uterine prolapse usually occurs in older women, but may also be present in younger women who had very large babies and a prolonged, difficult delivery. Extensive prolapse of the uterus may interfere with urination as well as with defecation. The usual treatment for uterine prolapse is surgical reattachment or, in more extreme cases, hysterectomy.

Abnormal (**dysfunctional**) **uterine bleeding** (**AUB**) may occur in adolescents who constitute as much as 20% of the cases, but most women who have been diagnosed with AUB are 40 years of age or older. This condition must be differentiated from vaginal bleeding that may occur if the woman is pregnant. AUB may be due to clotting defects; uterine tumors, fibroids, and polyps; hormonal imbalance; and a number of other conditions such as pelvic inflammatory disease, PCOS, endometriosis, anovulation, and even obesity. The common symptoms of AUB are irregular menstrual cycle (shorter or longer than the normal 21–35 days in adults or 21–45 days in women younger than 20 years), menstruation lasting for more than the normal 4 to 6 days, and heavy bleeding with or without blood clots. Treatment of AUB depends on the causative factors and may include prescribing birth control pills; removal of polyps, fibroids, and tumors; and, in extreme cases, hysterectomy.

V. CERVIX

A. The cervix does not participate in menstruation, but its *secretions change* during various stages of the menstrual cycle. Branched **cervical glands** secrete a serous fluid near the time of ovulation that facilitates the entry of spermatozoa into the uterine lumen. During pregnancy, cervical glands produce a thick, viscous secretion that hinders the entry of spermatozoa (and microorganisms) into the uterus.

B. The cervical wall is composed mainly of dense collagenous connective tissue interspersed with numerous elastic fibers and a few smooth muscle cells.

C. **The cervix has a simple columnar (*mucus-secreting*) *epithelium* except for the inferior portion (continuous with the lining of the vagina), which is covered by a *stratified squamous nonkeratinized epithelium*.**

D. **Prior to parturition, the cervix dilates and softens as a result of the lysis of the collagen fiber bundles in response to the hormone *relaxin*.**

CLINICAL CONSIDERATIONS

In a **Papanicolaou (Pap) smear**, epithelial cells are scraped from the lining of the cervix (or vagina) and are examined to detect cervical cancer. A Pap smear shows **variation in cell populations** with stages of the menstrual cycle. In 2017, the U.S. Preventive Services Task Force indicated that in women between 30 and 65 years of age, **human papilloma virus (HPV)** testing can be used once every 5 years, instead of the Pap smear and HPV test every 3 years. Prior to this recommendation, both Pap smear and HPV testing were used together. For women 21 through 29 years of age, a Pap smear is still recommended every 3 years. Of course, these recommendations are not to be considered as standard of care for each woman. Women should consult their gynecologists for what is best for them.

Carcinoma of the cervix originates from stratified squamous nonkeratinized epithelial cells. It may be contained within the epithelium and not invade the underlying stroma (**carcinoma in situ**), or it may penetrate the basal lamina and metastasize to other parts of the body (**invasive carcinoma**). It occurs at a relatively high frequency but may be cured by surgery if discovered early (by Pap smear), before it becomes invasive.

VI. FERTILIZATION AND IMPLANTATION

A. **Fertilization usually takes place within the ampulla *of the oviduct*; it occurs when a spermatozoon penetrates the corona radiata and the ZP and pierces the plasma membrane of a *secondary oocyte*.**

1. Before a spermatozoon is capable of fertilizing, it must undergo **maturation**, **capacitation**, and **hyperactivity**.
   a. **Maturation** occurs in the male reproductive tract. Prior to maturation the spermatozoon cannot travel in a forward direction, instead it travels only in a circular fashion.
   b. **Capacitation** occurs in the female reproductive tract. Although the sperm is in the male reproductive tract, it is unable to undergo capacitation because the concentration of the prostate-manufactured **fertilization promoting peptide (FPP)** is too high. Once the sperm arrives in the female reproductive tract, the concentration of FPP is reduced to a suitable level (because it becomes diluted by the vaginal secretions), and the sperm is prompted to begin the process of capacitation. This process requires the following three steps:
      (1) **Cholesterol molecules** are removed from the acrosomal plasmalemma, making the membrane less rigid.
      (2) Special **Ca^{2+} ion channels** open in the plasma membrane of the spermatozoon flagella, permitting the influx of calcium ions.
      (3) Elevated levels of intraflagellar calcium ions induce the formation of **cyclic adenosine monophosphate**, which causes the spermatozoon to become hyperactive.
   c. **Hyperactivity** is merely the ability of the spermatozoon to swim faster and more vigorously, making it easier for the sperm to penetrate the ZP to contact the oocyte.
2. Once the spermatozoon has undergone capacitation, it is capable of fertilizing the egg, but, in order to do so, it must undergo **acrosome reaction**, **bind to ZP 3** of the ZP, and **fuse to the plasma membrane of the secondary oocyte**.
   a. **The acrosome reaction** and **binding to ZP 3** occur when the spermatozoon contacts the ZP. Hydrolytic enzymes, especially **acrosin**, are released from the acrosome; acrosin reduces the viscosity of the ZP just ahead of the spermatozoon, permitting it to reach the secondary oocyte.

b. **Fusion** of the spermatozoon membrane and the secondary oocyte plasmalemma occurs due to the presence of **fertilin**, an integral protein in the spermatozoon membrane with **CD9 molecules** and **integrins** of the secondary oocyte's plasmalemma.

3. The **secondary oocyte** responds to the spermatozoon contact by undergoing **cortical reaction**, **resuming the second meiotic division**, and forming the **female pronucleus**.
   a. The **cortical granules** of the secondary oocyte, located just deep to the cell membrane, fuse with the cell membrane, releasing their enzymes into the ZP. The ZP proteins form a complex with each other that transforms the gelatinous nature of the ZP into a highly viscous substance that stops other spermatozoa from reaching the secondary oocyte, thus preventing **polyspermy**.
   b. The contact of spermatozoon with the secondary oocyte permits the entry of the **spermatozoon's nucleus** (**male pronucleus**) and **centrosome** into the secondary oocyte's cytoplasm, triggering the oocyte to **complete its second meiotic division**, forming the **second polar body** and thus transforming the secondary oocyte into the **ovum**.
   c. The now haploid nucleus of the ovum is known as the **female pronucleus**. The two haploid pronuclei travel toward each other and shed their nuclear envelopes; their chromosomes intermingle as they form a **diploid cell**, known as the **zygote**. Immediately after the intermingling of the chromosomes, the centrosome, contributed by the spermatozoon, forms a mitotic spindle apparatus, and the zygote undergoes its first mitotic division. The two newly formed daughter cells are the first two cells of the new embryo. Note that *all centrosomes of the new individual are derived from the father, and all of the mitochondria are derived from the mother.*

CLINICAL CONSIDERATIONS

Numerous **methods of contraception** exist, including birth control pills for females and for males; subdermal or intramuscular substances; barriers, such as female and male condoms, diaphragms, contraceptive sponges; contraceptive implants; emergency contraceptives, namely Levonelle; intrauterine devices (IUDs); and surgical procedures—for males, vasectomy, and for females, tubal ligation.

Female birth control pills are compounds containing estrogen and progestin that prevent ovulation but allow menstruation to occur. These pills must be taken every day for 21 days and then stopped to ensure that menstruation can occur. In order to ease their use, the first 21 pills are composed of the two hormones and the remaining pills are inert, so that the woman on the pill does not forget to resume the hormone pills after menstruation is over.

Male birth control pills are composed of androgens that shut off LH and FSH production and also prevent or greatly reduce sperm formation. Unfortunately, the male pill is much less effective than the female birth control pill.

Subdermal or intramuscular substances are composed of progestin that is injected into the woman, and it actively interferes with ovulation for as long as 3 months.

Female condoms are composed of polyurethane substances that line the vagina; **male condoms** are blindly ending sheaths, usually composed of latex, that are pulled over the penis to trap the spermatozoa. Frequently, they are fortified by a spermicidal agent.

The **diaphragm** is a device that is placed into the vagina and must be coated with a spermacide before sexual intercourse to prevent spermatozoa from entering the uterus. It has to be in place 6 or more hours prior to sex and removed and cleaned no later than 24 hours after placement.

Contraceptive sponges are round, small polyurethane sponges treated with spermicidal agents. They are placed in the vagina close to the cervix to prevent the sperm from gaining access to the uterus. The sponge should remain in the vagina for at least 6 hours after sex but for no longer than 24 hours after placement.

The contraceptive **implant** is implanted into the arm and releases progestin for a period of 3 years after which it must be taken out. It is the most effective method of temporary birth control.

Emergency contraception, known as the "morning after pill," which goes by the trade name Levonelle, protects against pregnancy if taken within 24 hours after sex. Within 24 hours, it is 95% effective.

IUDs are small, T-shaped structures that are placed by a gynecologist inside the uterus with the crossbar of the T near the openings of the oviducts and the stem of the T near the cervix. One type of IUD is infused with progestin, which is released slowly over a period of years. These are quite safe

but may not be used in women with breast cancer or liver disease or with a high risk of breast cancer. The second type of IUD is composed of copper and is not infused with progestin. Copper IUDs are not safe for women with copper allergy or with high copper concentration (Wilson disease). IUDs may be removed at any time by a physician if the woman wants to get pregnant. Depending on the IUD, it can remain in the uterus for as long as 10 years.

Surgical procedures involve **vasectomy** for males and **tubal ligation** for females. Almost always, these are nonreversible procedures.

B. Implantation

1. The **zygote** undergoes mitotic cell division (known as **cleavage** during the early stages of embryogenesis) and is transformed into a multicellular structure called a **morula**. During this transformation, over a 3-day period, the **conceptus** (the preimplantation embryo and its surrounding membranes) travels through the oviduct and eventually enters the uterus.
2. As the conceptus enters the uterus, it acquires a fluid-filled cavity and becomes a **blastocyst**.
3. The blastocyst implants in the endometrium of the uterus and is surrounded by an inner cellular layer, the **cytotrophoblast**, and an outer multinucleated layer, the **syncytiotrophoblast**.
4. The **syncytiotrophoblast** further invades the endometrium in the wall of the uterus by the sixth day after fertilization. Formation of the placenta then begins.

CLINICAL CONSIDERATIONS

Teratomas are germ cell tumors that fall into three groups: mature, monodermal, and immature.

Mature teratomas are benign (although occasionally they may become malignant) and are usually present in young women. These are cysts with walls that frequently contain hair and other epidermal structures such as sebaceous glands as well as bone, tooth, and cartilage fragments.

Monodermal teratomas are rare tumors that are also known as specialized teratomas. The two most frequent types of these tumors are struma ovarii and ovarian carcinoid. **Struma ovarii** is an ovarian tumor composed of well-developed thyroid follicles that produce thyroid hormone and may be responsible for hyperthyroidism. **Ovarian carcinoid** is a tumor that usually produces serotonin (5-OH-tryptamine).

Immature teratomas are fast-growing malignant tumors with a histology that resembles that of fetal rather than mature tissues. They are usually present in adolescents and very young women.

VII. PLACENTA

The placenta is a **transient** structure, consisting of a **maternal portion** and a **fetal portion**. At birth it is approximately 18 cm in diameter, 2.5 cm thick, and weighs about 600 g.

A. Structure

1. As the placenta begins its development, the **cytotrophoblasts** and **syncytiotrophoblasts** form the **chorion** and in response, the endometrium of the uterus forms the **decidua**. The chorion develops into the **chorionic plate,** which gives rise to the **chorionic villi**. The decidua has three regions, **decidua basalis**, **decidua capsularis**, and **decidua parietalis**, but only the decidua basalis forms the majority of the maternal portion of the placenta.
2. Maternal blood vessels invade the decidua basalis, forming large blood-filled spaces known as **lacunae**. Chorionic villi of the developing fetus become vascularized, and capillary beds form within the villi. The chorionic villi grow into the lacunae and receive nutrients and oxygen from and deliver waste products and carbon dioxide into the maternal blood of the lacunae.
3. This transfer of nutrients and waste products occurs across a barrier, the **placental barrier**, interposed between the maternal blood and fetal blood. The narrowest placental barrier is composed of the following:
   a. Endothelial cells of the fetal capillaries

table 17.2 Hormones Produced by the Placenta

Hormone	Cells Producing Hormone	Function of Hormone
hCG	Syncytiotrophoblasts and also cytotrophoblasts	Maintains corpus luteum
hCS (also known as human placental lactogen)	Syncytiotrophoblasts	Regulates glucose metabolism; stimulates proliferation of mammary gland duct
IGF-I and IGF-II	Cytotrophoblasts	Stimulates growth and proliferation of cytotrophoblasts
EGF	Early (4–5 weeks): cytotrophoblasts Late (6–12 weeks): syncytiotrophoblast	Stimulates development and maintains functions of trophoblasts
Relaxin	Decidual cells	Makes cervix and fibrocartilage of pubic symphysis more pliable for parturition
Leptin	Syncytiotrophoblasts	Controls maternal nutrient status and facilitates transport of nutrients across the placental barrier
Fibroblast growth factor	Syncytiotrophoblasts	Facilitates proliferation of cytotrophoblasts
Colony-stimulating factor	Syncytiotrophoblasts	Facilitates proliferation of cytotrophoblasts
Platelet-derived growth factor	Syncytiotrophoblasts	Facilitates proliferation of cytotrophoblasts
Interleukin 1	Syncytiotrophoblasts	Facilitates proliferation of cytotrophoblasts
Interleukin 3	Syncytiotrophoblasts	Facilitates proliferation of cytotrophoblasts
Tumor necrosis factor	Syncytiotrophoblasts	Inhibits proliferation of cytotrophoblasts

EGF, endothelial growth factor; hCG, human chorionic gonadotropin; hCS, human chorionic somatomammotropin; IGF-I and II, insulin-like growth factors I and II.

b. Basal lamina of the fetal capillary endothelium
c. Basal lamina of the cytotrophoblasts
d. Cytotrophoblasts
e. Syncytiotrophoblasts

4. The presence of connective tissue elements between the two basal laminae enlarges the thickness of the placental barrier.

B. Function (Table 17.2)

1. The placenta permits the exchange of various materials between the maternal and fetal circulatory systems. This exchange occurs **without** mixing of the two separate blood supplies.
2. The placenta secretes **progesterone**, **hCG**, **chorionic thyrotropin**, and **hCS**, a lactogenic and growth-promoting hormone as well as endothelial growth factor, insulin-like growth factors I and II, fibroblast growth factor, colony-stimulating factor, platelet-derived growth factor, tumor necrosis growth factor, relaxin, leptin, and interleukins 1 and 3.
3. It also produces **estrogen** with the assistance of the liver and adrenal cortex of the fetus.
4. Decidual cells of the stroma produce **prostaglandins** and **prolactin**.

CLINICAL CONSIDERATIONS

For a long time, the **placenta** was believed to be a sterile organ; however, recent studies have demonstrated that the placenta–uterus interface and the region of the placenta that faces the embryo have a low-abundant but specific microbiome. Surprisingly, when the bacterial population of the placenta was compared to those of the skin, nasal cavity, gastrointestinal tract, vagina, and the oral cavity, the microbiome of the oral cavity was most similar to the placenta's bacterial population. In fact, the phyla located on the tongue, in gingival plaques, and on the tonsils closely resembled the placental load. These included members of *Bacteroidetes*, *Firmicutes*, *Fusobacteria*, *Proteobacteria*, and *Tenericutes*. These microorganisms are believed to reach the placenta through the vascular supply. These findings suggest that pregnant women should ensure that they have good oral hygiene, especially because the presence of periodontal disease in pregnant women has been correlated with premature birth.

Preeclampsia (previously termed **toxemia**) is a dangerous condition in which pregnant women without a history of hypertension suddenly present with high blood pressure (>140/90) and with proteinuria relatively late in the pregnancy. Other symptoms of preeclampsia that occur frequently include swollen extremities, sudden and unwanted increase in weight, nausea, vomiting, abdominal pain, relentless headaches, and problems with urination. If preeclampsia is untreated, the condition may progress to **eclampsia** with accompanying seizures. Unfortunately, some individuals do not display any of the self-observable symptoms, but even those women can be diagnosed through measuring blood pressure and urine tests, making it important for the pregnant woman to see her gynecologist/obstetrician on a regular basis. Although the precise origins of preeclampsia are not known, the condition has been amply demonstrated to be due to defects in the placenta, probably as a function of problems with the placental blood supply. Predisposing factors, some of which are genetic, in the development of preeclampsia include hypertension prior to pregnancy, previous history of preeclampsia, obesity, and carrying twins or triplets. If the condition is severe and if the baby's development is advanced enough, then a prompt delivery is indicated. If the baby has not developed to the extent that it is safe to deliver the child, then the patient should remain under close observation until delivery is either safe for the baby or delivery of the baby is to protect the life of the mother. The symptoms of preeclampsia resolve within a few weeks after delivery of the child and removal of the placenta.

VIII. VAGINA

A. **The vagina, a *fibromuscular canal* with a wall that is composed of three layers, an inner *mucosa*, a middle *muscularis*, and an external *adventitia*, is circumscribed by a *skeletal muscle* sphincter at its external orifice.** It lacks glands throughout its length and is lubricated by secretions from the cervix and by seepage of the extracellular fluid from the vascular supply of the lamina propria.
   1. The **mucosa** is composed of a thick, **stratified squamous nonkeratinized epithelium** and a fibroelastic connective tissue, the **lamina propria**.
      a. The **epithelium** contains **glycogen**, which is used by the vaginal bacterial flora to produce **lactic acid**, an acid that lowers the pH during the follicular phase of the menstrual cycle and inhibits invasion by pathogens.
      b. The **lamina propria** is a fibroelastic connective tissue that is **highly vascular** in its deeper aspect (which is possibly analogous to a submucosa).
   2. The **muscularis** is composed of irregularly arranged layers of **smooth muscle** (thin inner circular layer and a thicker outer longitudinal layer) interspersed with **elastic fibers**.
   3. The **adventitia** is composed of **fibroelastic** connective tissue. It attaches the vagina to the surrounding structures.

IX. EXTERNAL GENITALIA (VULVA)

A. **The labia majora are *fat-laden folds of skin*; *hair* and secretions of *sebaceous glands* and *sweat glands* are present on their external surfaces.**

B. **The labia minora, folds of skin that possess a core of *highly vascular* connective tissue containing elastic fibers, lack hair follicles, but their dermis contains numerous *sebaceous glands*, which open directly onto the epithelial surface.**

C. **The vestibule is the space between the two labia minora. Glands of Bartholin (mucus-secreting glands) and numerous smaller mucus-secreting glands around the urethra and clitoris (minor vestibular glands) open into this space.**

D. The clitoris, composed of two small, cylindrical *erectile bodies*, which terminate in the prepuce-covered *glans clitoridis*, contains many sensory nerve fibers and specialized nerve endings (e.g., Meissner corpuscles and Pacinian corpuscles).

X. MAMMARY GLANDS

Mammary glands of both genders are identical for the first decade or so of life, but, when the female reaches puberty, the flow of estrogen and progesterone as well as lactogenic hormone induces the mammary gland to enlarge and develop a system of lobules and terminal ductules as well as an increase in the connective tissue mass and a deposit of adipose tissue. Each mammary gland of the postpubertal female is composed of numerous **compound tubuloacinar (tubuloalveolar) glands**, each with its own lactiferous sinus and a duct that opens at the apex of the nipple.

CLINICAL CONSIDERATIONS

The use of lavender oil and tea tree oil–based products in prepubescent males has been shown to cause gynecomastia, the development of breasts in these individuals. The presence of the breast tissue persisted for several months after the boys stopped using these products and then slowly regressed to its normal condition. These oil products appear to be able to imitate and even inhibit the effects of androgens.

The polypeptide hormone **prolactin**, manufactured by acidophils of the adenohypophysis (anterior pituitary), causes an increase in breast size in the pregnant female and induces milk formation as well as lactation in the mammary glands of the postpartum female. Interestingly, it also causes the feeling of sexual gratification subsequent to the sexual act. Because prolactin has been shown to alleviate the symptoms of multiple sclerosis (MS) in the pregnant female, recent investigations using a mouse model demonstrated that treatment of MS-afflicted mice with prolactin resulted in remyelination of nerve fibers, whose myelin was destroyed by the disease. Prolactin is believed to stimulate the formation of pro-oligodendrocytes, which differentiate into oligodendrocytes, cells that are responsible for myelination of axons in the central nervous system.

A. Nonlactating (resting) mammary glands (in adult, nonpregnant women) are composed of *lactiferous sinuses* and *ducts* lined in most areas by a stratified cuboidal epithelium, with a basal layer consisting of scattered *myoepithelial cells*. A basal lamina separates the epithelial components from the underlying stroma.

B. Lactating (active) mammary glands are enlarged during pregnancy by the development of acini (*alveoli*) (Fig. 17.7).

1. **Alveolar cells (secretory cells)** (Fig. 17.8) line the alveoli of active mammary glands and are surrounded by an incomplete layer of **myoepithelial cells**. They are richly endowed with RER and contain several Golgi complexes, numerous mitochondria, lipid droplets, and vesicles containing milk protein (caseins) and lactose.
2. **Secretion by alveolar cells**
   a. **Lipids** are released into the lumen, perhaps via the **apocrine** mode of secretion.
   b. **Proteins** and sugars are released into the alveolar lumen via the **merocrine** mode of secretion (exocytosis).

C. The nipple, composed of dense, irregular collagenous connective tissue interlaced with smooth muscle fibers that act as a *sphincter*, contains the openings of the *lactiferous ducts*. It is surrounded by pigmented skin (**areola**) that is more deeply pigmented during and subsequent to pregnancy and contains the **areolar glands (of Montgomery)**.

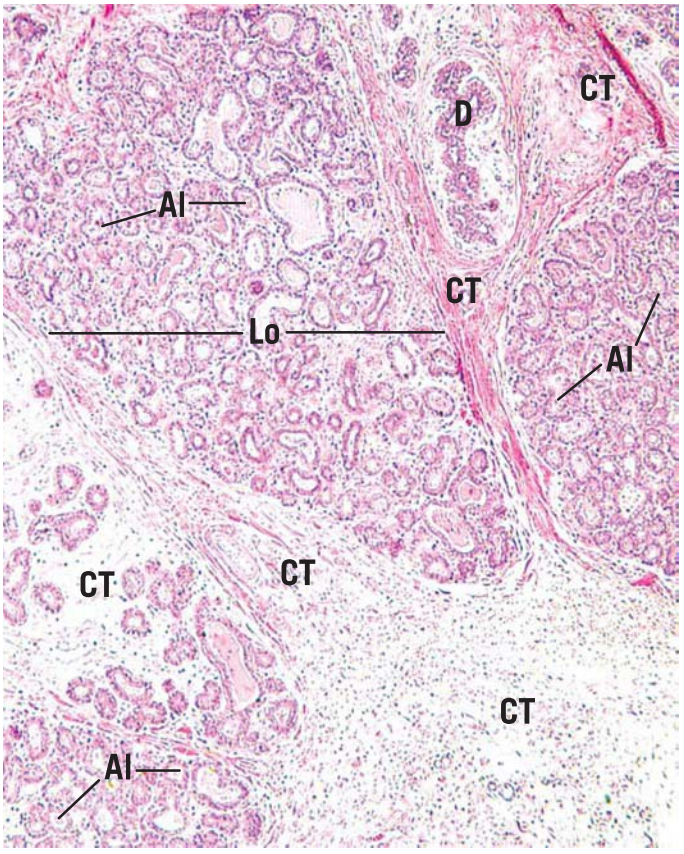


FIGURE 17.7. This low-magnification photomicrograph of a lactating mammary gland displays connective tissue septa (CT) that envelope lobes (Lo) of the mammary gland. Note that the alveoli (Al) are filled with milk, the secretory product of the lactating mammary gland. Ducts (D) deliver the milk to the lactiferous sinuses and then to the lactiferous ducts of the nipple (×132).

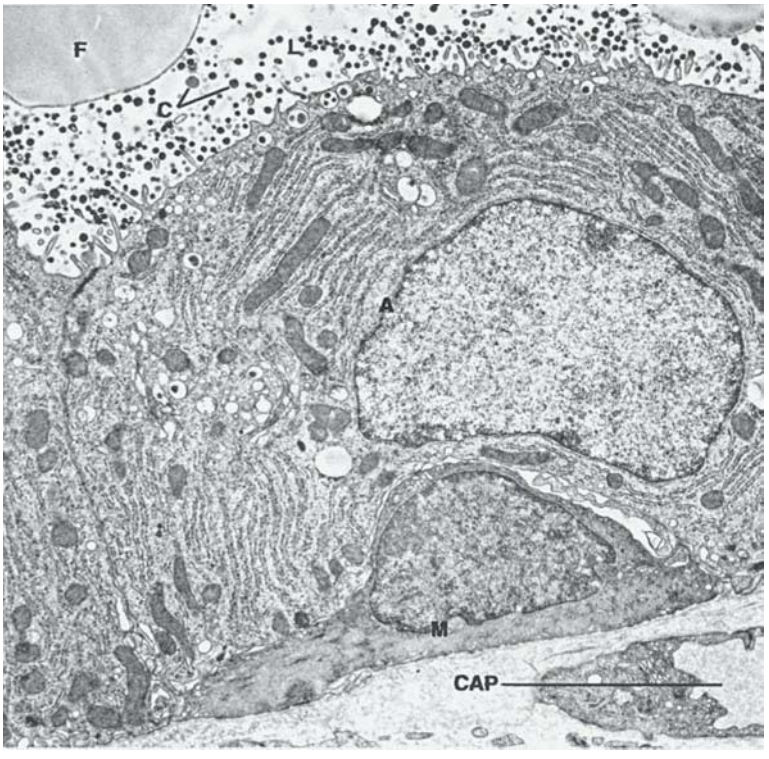


FIGURE 17.8. Transmission electron micrograph showing an alveolar epithelial cell (A) from a lactating mammary gland and an underlying myoepithelial cell (M). C, casein; CAP, capillary; F, fat droplet; L, lumen of alveolus containing milk. (Reprinted with permission from Strum J. *A Study of Electron Micrographs.* 3rd ed. Baltimore, MD: University of Maryland School of Medicine; 1992:105.)

CLINICAL CONSIDERATIONS

Breast cancer may originate from the epithelium lining the ducts (**ductal carcinoma**) or the terminal ductules (**lobular carcinoma**). If breast cancer is not treated early, the tumor cells **metastasize** via lymphatic vessels to the axillary nodes near the affected breast and later via the bloodstream to the lungs, bone, and brain. In the United States, 180,000 new cases of breast cancer are diagnosed annually, and every year, 43,000 women die of this disease. **Early detection** by self-examination, mammography, or ultrasound has led to a reduction in the mortality rate associated with breast cancer. The symptoms of breast cancer that every woman should know include lumps in the breast tissue; pitting of the skin covering the breast; and change in the appearance of the nipple, areola, and the breast. Although both males and females can develop breast cancer, females have a much greater chance of developing the condition. Of the various types of breast cancer, the following are the most common:

Invasive ductal carcinoma, the most common form of breast cancer amounting to almost 80% of the breast cancer cases, is derived from the ducts of the mammary gland, but the cancerous cells have migrated usually only to nearby tissues of the body (this is the type of breast cancer that is also present in males).

Ductal carcinoma in situ is noninvasive and involves only the ducts of the mammary glands.

A condition known as **lobular carcinoma in situ** is a precancerous form of mammary gland tumor and is composed of small, individual cells that are found in clusters in the breast tissue. Most clinicians do not treat these patients, but keep them under close observation because the possibility of the condition becoming malignant places these women in a higher risk category.

Metastatic breast cancer is one of the most fatal types of breast cancer because the malignant cells have metastasized via blood and/or lymph circulatory systems to the bony skeleton, brain, lungs, and/or liver.

Fortunately, **inflammatory breast cancer**, a very virulent form of breast cancer, is not very common. This form of breast cancer does not form recognizable lumps. The malignant cells block lymph vessels, the breast becomes inflamed and warmer than the other parts of the body, the skin over the breast may resemble an orange peel, and the nipple may suddenly become inverted.

Unlike the malignant cells of other breast cancers, those of **triple-negative breast cancer** do not have estrogen, progesterone, or HER2/neu (family of epidermal growth factor) receptors. The lack of these receptors prevents the use of hormone therapy or the use of drugs that block these hormones. Patients with this type of breast cancer have mutations in the *BRCA1* gene and respond well to chemotherapy if treated early in the onset of the cancer. Treatments during the later stages of triple-negative breast cancer are not nearly as effective, and the aggressive nature of the tumor causes it to reappear.

The role of the *BRCA1* and *BRCA2* **gene products** is to force cells into apoptosis if damage to their DNA cannot be repaired. Both of these genes are normally expressed in a number of cell types in the body, but especially in the cells of the breast. Therefore, these two genes are referred to as **human tumor-suppressor genes**, and their products are referred to as **breast cancer type 1 susceptibility protein** and **breast cancer type 2 susceptibility protein**, respectively. Mutations in these two genes dispose their carrier to a very high probability of developing cancer of the breast and cancer of the ovary.

Deficiency or mutation in ***BRCA1*** has been shown to decrease the stability or elevate the incidence of the mutation rate of **tumor-suppressor genes** such as ***p53*. Mutations in the *BRCA1* gene** appear to result in incapacitation of the checkpoint at G_2-M of the cell cycle, and concurrently, the number of centrosomes of these cells is increased. Therefore, these mutated cells have the capability to proliferate unchecked. Defective gene products of the *BRCA1* gene have been reported to be responsible for an equal probability of resulting in breast cancer but more than twice the probability of developing ovarian cancer as mutations in the *BRCA2* gene.

Certain mutations in the ***BRCA2* gene** produce defective gene products that can prevent the cell from repairing double-stranded DNA breaks, thereby not only increasing the possibility of the development of breast cancer in the individual, but, depending on the gender, may also increase the risk of ovarian, oviduct, and prostate cancer. Additionally, some of these mutations may also be responsible for an increased incidence of melanoma and cancer of the pancreas as well as of other malignancies.

Women who have a family history of breast and/or ovarian cancer should be tested for mutations in the *BRCA1* and *BRCA2* genes, especially if a close relative with breast/ovarian cancers has been shown to have mutations in these genes.

Percent of Women Developing Breast or Ovarian Cancers with or without Gene Mutations

Cancer Type	No mutations	BRCA1 Mutation	BRCA2 Mutation
Breast	12% of women	60% of women	45% of women
Ovarian	1.5% of women	40% of women	15% of women

D. Secretions of the mammary glands

1. The **colostrum** (**protein-rich yellowish fluid**), produced during the first few days after birth, is rich in cells (mainly lymphocytes and monocytes), lactalbumin, fat-soluble vitamins, and minerals and contains **immunoglobulin A** (**IgA**).
2. **Milk** begins to be secreted by the third or fourth day after birth.
   a. It consists of proteins (caseins, IgA, lactalbumin), many lipid droplets, and lactose.
   b. Milk is released from the mammary glands via the **milk ejection reflex** in response to a variety of external stimuli related to suckling. The milk ejection reflex involves release of **oxytocin** (from axons in the pars nervosa of the pituitary gland), which induces contraction of the **myoepithelial cells**, forcing milk into the larger ducts and out of the breast.

Review Test

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or completions of the statement. Select the ONE lettered answer that is BEST in each case.

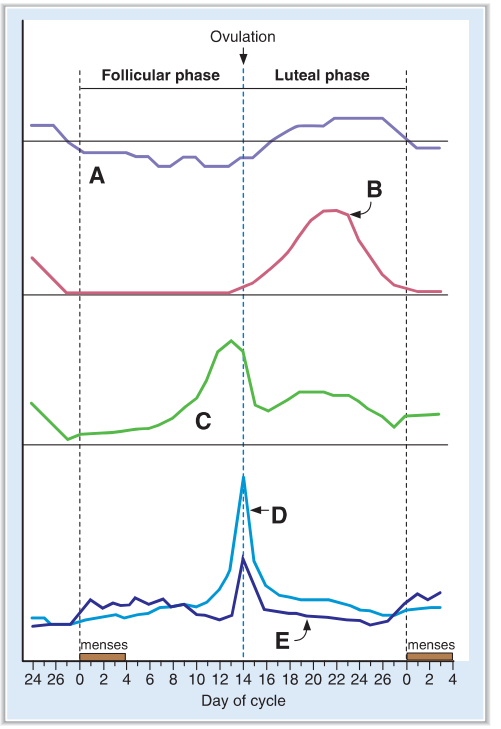
1. A mother who delivered her baby a few days ago has not started to release her colostrum; therefore, the baby is missing the antibody that is present in the milk. Which antibody is missing?

(A) IgA
(B) IgD
(C) IgE
(D) IgG
(E) IgM

2. A woman was diagnosed with a malignant, fast-growing teratoma. What is the most likely subtype?

(A) Mature teratoma
(B) Monodermal teratoma
(C) Immature teratoma
(D) Struma ovarii
(E) Ovarian carcinoid

Questions 3 to 6 refer to the following figure:



3. Which graph represents the causative agent that triggers primary oocyte to complete meiosis I?

(A) A
(B) B
(C) C
(D) D
(E) E

4. Which graph in the above figure details progesterone levels during the menstrual cycle?

(A) A
(B) B
(C) C
(D) D
(E) E

5. Which graph in the above figure details FSH levels during the menstrual cycle?

(A) A
(B) B
(C) C
(D) D
(E) E

6. Which graph in the above figure details basal body temperature levels during the menstrual cycle?

(A) A
(B) B
(C) C
(D) D
(E) E

7. A woman who was diagnosed with a form of breast cancer is told that she does not require treatment but she will be kept under close observation. What is the most probable diagnosis?

(A) Metastatic breast cancer
(B) Invasive ductal carcinoma
(C) Ductal carcinoma in situ
(D) Lobular carcinoma in situ
(E) Inflammatory breast cancer

8. A prepubescent boy is seen by his pediatrician because he has been using lavender oil–based products. What caused his parents to be concerned?

(A) He was caught masturbating.
(B) He developed hair in his axilla.
(C) He developed breasts.
(D) He had a serious case of acne.
(E) He had an erection lasting several hours.

9. The placental microbiome is most similar to that of which body region?

(A) Nares
(B) Vagina
(C) Oral cavity
(D) Gastrointestinal tract
(E) Skin

10. A woman sees her gynecologist for an annual visit and tells her about a sharp pain that occurs every month in her abdominal region about 2 weeks after her menstrual bleeding stopped. In the absence of any pathologies upon examination, what is the most likeable source of the pain?

(A) Kidney stones
(B) Mittelschmerz
(C) Gall stones
(D) Skeletal muscle cramps
(E) Abdominal bloating

Answers and Explanations

1. **A.** IgA antibodies are present in colostrum and milk. IgG antibodies are acquired by the fetus by placental transfer from the mother.
2. **C.** Immature teratomas are fast-growing malignant tumors. The other teratomas listed are usually benign, but even those that do become malignant are slow growing.
3. **D.** The level of LH during the menstrual cycle is represented by graph D.
4. **B.** The level of progesterone during the menstrual cycle is represented by graph B.
5. **E.** The level of FSH during the menstrual cycle is represented by graph E.
6. **A.** The basal body temperature levels during the menstrual cycle is represented by graph A.
7. **D.** Lobular carcinoma in situ is a precancerous form of mammary gland tumor and is composed of small, individual cells that are found in clusters in the breast tissue. Most clinicians do not treat these patients, but keep them under close observation because the possibility of the condition becoming malignant places these women in a higher risk category.
8. **C.** The use of lavender oil and tea tree oil–based products in prepubescent males has been shown to cause gynecomastia, the development of breasts in these individuals. The presence of the breast tissue persisted for several months after the boys stopped using these products and then slowly regressed to its normal condition. These oil products are apparently able to imitate and even inhibit the effects of androgens.
9. **C.** For a long time, the placenta was believed to be a sterile organ; however, recent studies have demonstrated that the placenta–uterus interface and the region of the placenta that faces the embryo have a low-abundant but specific microbiome. Surprisingly, when the bacterial population of the placenta was compared with those of the skin, nasal cavity, gastrointestinal tract, vagina, and the oral cavity, the microbiome of the oral cavity was most similar to the placenta's bacterial population. In fact, the phyla located on the tongue, in gingival plaques, and on the tonsils closely resembled the placental load. These included *Bacteroidetes*, *Firmicutes*, *Fusobacteria*, *Proteobacteria*, and *Tenericutes*.
10. **B.** Some women experience a sudden abdominal (or pelvic) pain in the middle of their menstrual cycle (mittelschmerz) that lasts 2 or 3 hours (although it may last as long as 48–72 hours or even longer), and they have attributed that to the process of ovulation. Although this attribution was not universally accepted, the sudden surge of LH is now known to be followed by a similar surge in prostaglandin F_{2a}, a pharmacologic agent that causes sudden, cramp-like contraction of the ovarian, fallopian tube, or uterine smooth muscle fibers. This violent contraction is responsible for the pain experienced by some women. Other causes, such as painful distension of the ovarian follicles or the rupture of the tunica albuginea of the ovary, may also contribute to the ovulation pain.

chapter 18

Male Reproductive System

I. OVERVIEW—MALE REPRODUCTIVE SYSTEM

A. **The male reproductive system consists of the *testes*, *genital ducts*, accessory genital glands (*seminal vesicles*, *prostate gland*, and *bulbourethral glands*), and the *penis*.**

B. **Function. The male reproductive system produces *spermatozoa* (sperm), *testosterone*, and *seminal fluid*.** Seminal fluid transports and nourishes the sperm as they pass through the excretory ducts. The penis delivers sperm to the exterior and also serves as the conduit for excretion of urine from the body.

C. **Embryonic development of the gonads is a function of the *SRY gene* (sex-determining region on the Y chromosome).** If the Y chromosome is present, the *SRY gene* is expressed producing the **SRY protein**, which is the **testis-determining factor**, resulting in the formation of testes. In the absence of the Y chromosome, ovaries will develop.

II. TESTES

The paired testes develop in the posterior wall of the abdominal cavity and later descend into the scrotum, where they are suspended at the ends of the **spermatic cords**. They are the sites of **spermatogenesis** and production of the male **sex hormones**, primarily **testosterone** (Fig. 18.1).

CLINICAL CONSIDERATIONS

Cryptorchidism is a developmental defect characterized by failure of the testes to descend into the scrotum. The chance of this happening in full-term births is 1%, whereas it rises to a 30% chance in premature births. This condition results in sterility because the temperature of the undescended testes (i.e., normal body temperature) inhibits spermatogenesis; however, it does not affect testosterone production. It is associated with a much higher incidence of testicular malignancy than in normally descended testes. Cryptorchidism can be surgically corrected. In order to avoid complications later on in life, the usual recommendation is that the surgery be performed prior to the age of 1 year, assuming that the child is healthy enough for the procedure. The primary cause of this condition is not known (except in the small number of cases with a familial predisposition); however, several possible causes have been suggested, including testosterone deficiency during testicular development; defects in the length of the spermatic cord that prevent normal descent; and lack of formation of the gubernaculum, a fibromuscular ribbon that extends from the testes to the floor of the scrotum and probably assists in dragging the testis into the scrotum during the seventh month of embryonic development.

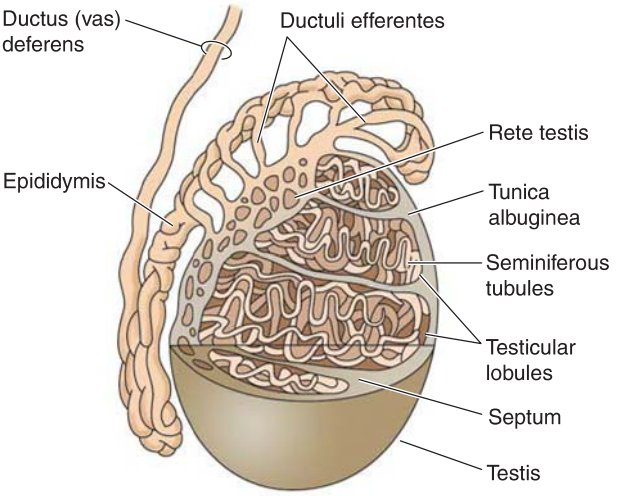


FIGURE 18.1 The testis and epididymis. (Reprinted with permission from Gartner LP. *Textbook of Histology*. 4th ed. Philadelphia, PA: Elsevier; 2017.)

A. Testicular tunicae (covering of the testes) are applied to the testes as they descend through the abdominal wall to enter the scrotum.

1. The **tunica vaginalis** is a **serous sac** derived from the peritoneum that partially covers the anterior and lateral surfaces of each testis.
2. **Tunica albuginea**, the thick, fibrous connective tissue capsule of the testis, is lined by a highly vascular layer of loose connective tissue, the **tunica vasculosa**. It is thickened posteriorly to form the **mediastinum testis**, from which incomplete connective tissue septa arise to divide the organ into approximately 250 compartments (lobuli testis). Additionally, the mediastinum testis is the passageway for blood and lymphatic vessels in and out of the testes.

B. The lobuli testes (see Fig. 18.1) are pyramidal intercommunicating compartments that are separated by incomplete septa. Each lobule contains one to four **seminiferous tubules** where spermatozoa are produced. These highly convoluted tubules are embedded in a meshwork of loose connective tissue containing blood and lymphatic vessels, nerves, and interstitial cells of Leydig.

C. Interstitial cells of Leydig, round to polygonal cells in the interstitial regions between seminiferous tubules, possess a large central nucleus, numerous mitochondria, a well-developed Golgi complex, and many lipid droplets. The lipid droplets contain cholesterol esters, precursors of testosterone.

1. Interstitial cells of Leydig, richly supplied with capillaries and lymphatic vessels, are **endocrine cells** that produce and secrete **testosterone**. Secretion is stimulated by **luteinizing hormone** (LH; interstitial cell–stimulating hormone) produced in the pituitary gland. These cells mature and begin to secrete during puberty.

D. Seminiferous tubules (Fig. 18.2), 30 to 70 cm long, with a diameter of 150 to 250 µm, are enveloped by a fibrous connective tissue tunic composed of several layers of fibroblasts and extensive capillary beds. They form tortuous pathways through the testicular lobules and then narrow into short, straight segments, the **tubuli recti,** which connect with the **rete testis.** The lumina of the seminiferous tubules are lined by a thick complex epithelium (**seminiferous** or **germinal epithelium**). This epithelium consists of four to eight cell layers and contains **spermatogenic cells**, from which the germ cells eventually develop (spermatogenesis), and **Sertoli cells**, which have several functions.

1. **Sertoli cells** (Fig. 18.3; also see Fig. 18.2) are columnar cells that extend from the basal lamina to the lumen of the seminiferous tubule. They have a pale, oval nucleus that displays frequent indentations; they are highly infolded and possess a large nucleolus. Sertoli cells no longer undergo mitosis after puberty.
   a. Their lateral plasma membranes have long processes that interdigitate with those of neighboring Sertoli cells, enfolding small clusters of developing spermatogenic cells. Their apical

FIGURE 18.2 Light micrograph of the seminiferous tubules in the testis (×132). Observe myoid cells (Mc) and fibrocytes (F) composing the wall of the seminiferous tubules. Spermatogonia (Sg) and the basal aspects of Sertoli cells (SC) lie in the basal compartment. In the adluminal compartment are primary spermatocytes (P). Note that spermatids (S) are located near the lumen.

cell membranes are highly convoluted forming finger-like processes where the interstices between these processes are occupied by developing spermatozoa.

b. They have a well-developed smooth endoplasmic reticulum, some rough endoplasmic reticulum (RER), an abundance of mitochondria and lysosomes, and an extensive Golgi complex.

c. Receptors for follicle-stimulating hormone (FSH) are present on their basal plasma membranes.

d. They form **zonulae occludentes** (tight junctions) with adjacent Sertoli cells near their bases, thus dividing the lumen of the seminiferous tubule into a **basal** and an **adluminal compartment**. These tight junctions are responsible for the **blood–testis barrier**, which protects developing sperm cells from autoimmune reactions.

e. **Function.** Sertoli cells support, protect, and nourish the spermatogenic cells and establish a **blood–testis barrier**. They not only phagocytose excess cytoplasm discarded by maturing spermatids but also secrete a fructose-rich fluid into the lumen that nourishes and facilitates the transport of spermatozoa through the seminiferous tubules to the genital ducts.

(1) Additionally, they synthesize **androgen-binding protein (ABP)** under the influence of FSH. **ABP** assists in maintaining the necessary concentration of testosterone in the seminiferous tubule so that spermatogenesis can progress.

(2) They secrete **inhibin**, a hormone that inhibits the synthesis and release of FSH by the anterior pituitary, as well as the hormone **activin**, which boosts FSH release from the anterior pituitary.

(3) During fetal development, they synthesize and release **anti-Müllerian hormone (Müllerian-inhibiting substance)**, which suppresses female genital ductal development.

(4) They manufacture and release **testicular transferrin**, a protein that facilitates the transfer of iron from **serum transferrin** to maturing spermatogenic cells.

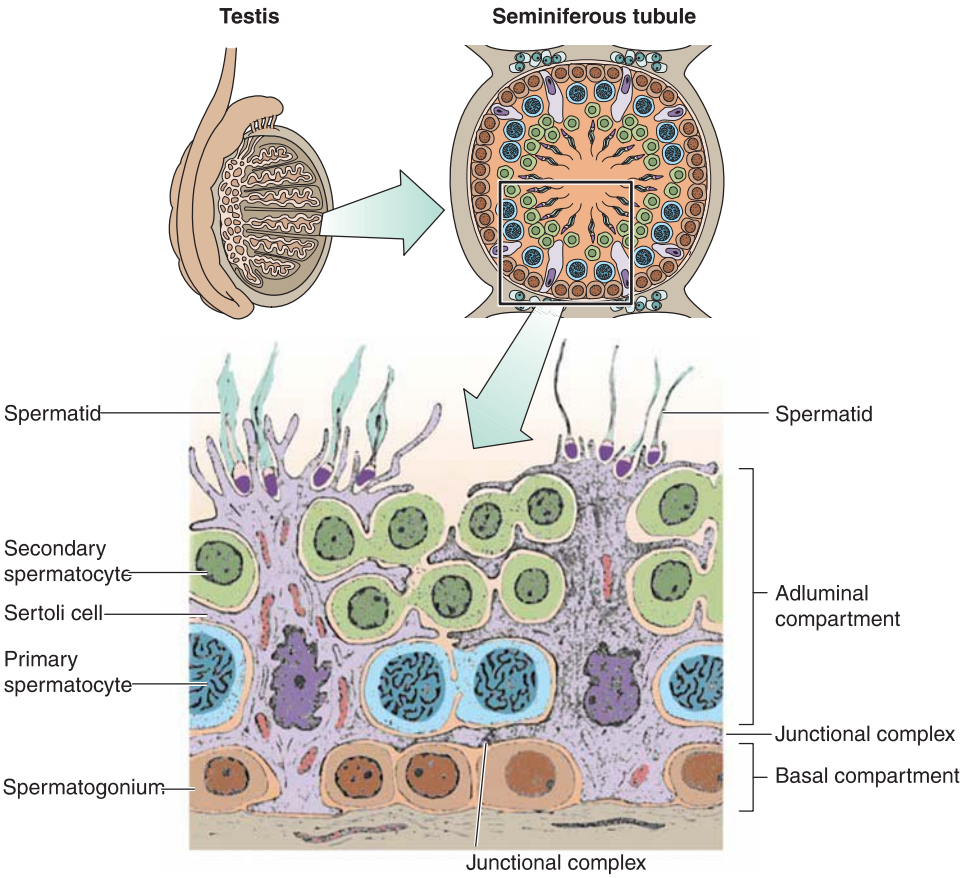


FIGURE 18.3 The seminiferous (germinal) epithelium. Note the intercellular bridges between spermatocytes and the junctional complexes near the bases of adjacent Sertoli cells. These junctional complexes of the Sertoli cells divide the epithelium into an adluminal and a basal compartment. (Reprinted with permission from Krause WJ, Cutts JH. *Concise Text of Histology*. 2nd ed. Baltimore, MD: Williams & Wilkins; 1986:414.)

2. **Spermatogenesis**
   a. **Shortly before puberty, the rise in gonadotrophins initiates spermatogenesis, the process of spermatozoon (sperm) formation.** It is divided into three phases: spermatocytogenesis, meiosis, and spermiogenesis (Table 18.1).
   b. Spermatogenesis does **not** occur simultaneously or synchronously in all seminiferous tubules, but rather in wave-like sequences of maturation, referred to as **cycles of the seminiferous epithelium**.
   c. During spermatogenesis, daughter cells remain connected to each other via **intercellular bridges**. The resultant **syncytium** may be responsible for the **synchronous development** of germ cells along **any one** seminiferous tubule.
3. **Spermatogenic cells** (see Fig. 18.2 and Table 18.2) are of three types: **spermatogonia**, **diploid** germ cells adjacent to the basal lamina of the seminiferous epithelium, which, at puberty, are influenced by testosterone to enter the cell cycle; **spermatocytes**; and **spermatids**.

table 18.1 Phases of Spermatogenesis

Spermatocytogenesis	Differentiation of spermatogonia into primary spermatocytes
Meiosis	Division to reduce the diploid chromosomal complement of primary spermatocytes to form haploid spermatids
Spermiogenesis	Transformation of spermatids into spermatozoa

table 18.2 Spermatogenic Cell Types and Their Characteristics

Spermatogonia	
Pale type A spermatogonia	Possess a pale-staining nucleus, spherical mitochondria, a small Golgi complex, and abundant, free ribosomes **Mitotically active** (starting at puberty) and give rise either to more cells of the same type (to maintain the supply) or to type B spermatogonia
Dark type A spermatogonia	Represent mitotically **inactive** (reserve) cells (in the G_0 phase of the cell cycle) with dark nuclei Have the potential to resume mitosis and produce pale type A cells
Type B spermatogonia	Undergo mitosis and give rise to primary spermatocytes
Spermatocytes	
Primary spermatocytes	Large **diploid** cells with 4cDNA content Undergo the **first meiotic division** (reductional division) to form secondary spermatocytes
Secondary spermatocytes	**Haploid** cells with 2cDNA that quickly undergo the **second meiotic division** (equatorial division), without an intervening S phase, to form spermatids
Spermatids	
Spermatids	Small **haploid** cells (containing only **1cDNA**) located near the lumen of the seminiferous tubule that possess a pair of centrioles, mitochondria, free ribosomes, SER, and a well-developed Golgi complex Nuclei often display regions of condensed chromatin

4. **Spermiogenesis** is a unique process of **cytodifferentiation**, whereby **spermatids** shed much of their cytoplasm and **transform into spermatozoa**, which are released into the lumen of the seminiferous tubule. Spermiogenesis is divided into four phases.
   a. The **Golgi phase** is characterized by the formation of an **acrosomal granule**, enclosed within an **acrosomal vesicle**, which becomes attached to the anterior end of the nuclear envelope of a spermatid; the centrioles migrate away from the nucleus to form the **flagellar axoneme**. Centrioles then migrate back toward the nucleus to assist in forming the **connecting piece** associated with the tail.
   b. The **cap phase** is characterized by expansion of the acrosomal vesicle over much of the nucleus, forming the **acrosomal cap.**
   c. The **acrosomal phase** is characterized by the following:
      (1) The **nucleus** becomes condensed, flattened, and located in the head region and the mitochondria aggregate around the proximal portion of the flagellum, which develops into the middle piece of the tail.
      (2) The **spermatid** elongates; this process is aided by a temporary cylinder of microtubules called the **manchette**.
      (3) The acrosomal phase ends as the spermatid is oriented with its acrosome, pointing toward the base of the seminiferous tubule.
   d. The **maturation phase** is characterized by loss of excess cytoplasm and intercellular bridges connecting spermatids into a syncytium. The discarded cytoplasm is phagocytosed by Sertoli cells. The maturation phase ends when the **nonmotile** spermatozoa are released (tail first) into the lumen of the seminiferous tubule. Spermatozoa remain immotile until they leave the epididymis. They become **capacitated** (capable of fertilizing) in the female reproductive system.
5. **Spermatozoon**
   a. The **head of the spermatozoon** (Fig. 18.4) is flattened and contains a dense, homogeneous nucleus with 23 chromosomes (22 plus the Y chromosome or 22 plus the X chromosome).
      (1) The spermatozoon head also possesses the acrosome, which contains **hydrolytic enzymes** (e.g., acid phosphatase, acrosin, neuraminidase, hyaluronidase, and proteases). As the spermatozoon penetrates the corona radiata, the acrosomal membrane fuses with the spermatozoon head's membrane, forming small openings through which some of the enzymes are released from the acrosome, assisting the sperm in reaching the zona pellucida (ZP) of the oocyte (see Chapter 17). As the spermatozoon head reaches the ZP, the glycoprotein ZP3 contacts the head of the spermatozoon, causing the acrosome to release all of its enzymes, a process known as the **acrosome reaction**.
   b. The **tail of the spermatozoon** includes the neck, middle piece, principal piece, and the end piece.

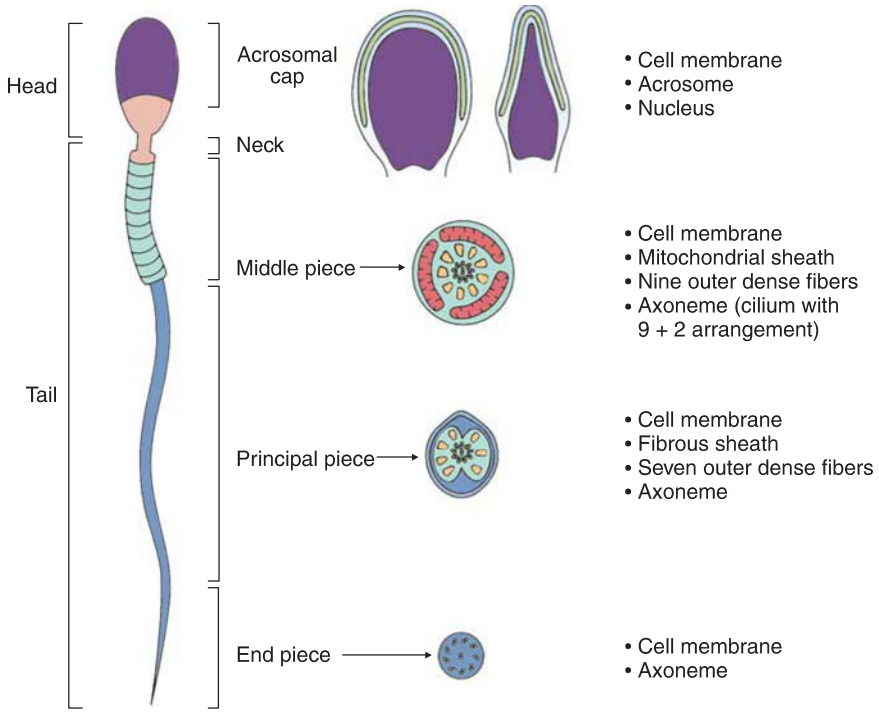


FIGURE 18.4 A human sperm. Regions of the mature sperm are shown on the left. Diagrams of sections through the head and the major segments of the tail are shown on the right. (Reprinted with permission from Henrikson RC, Kaye GI, Mazurkiewicz JE. *Histology National Medical Series for Independent Study*. Baltimore, MD: Williams & Wilkins; 1997:399.)

(1) The **neck** includes the centrioles and the **connecting piece**, which is attached to the nine **outer dense fibers** of the remainder of the tail.

(2) The **middle piece** extends from the neck to the **annulus** and contains the axoneme, nine outer dense fibers, and a spirally arranged **sheath of mitochondria**.

(3) The **principal piece** extends from the annulus to the end piece and contains the axoneme with its surrounding dense fibers, which, in turn, are encircled by a **fibrous sheath** that has circumferential ribs.

(4) The **end piece** consists of the axoneme and the surrounding plasma membrane. Recent studies, using the technique of cryoelectron tomography, have demonstrated the presence of left-handed helical spiral nanostructures, named **tail axoneme intra-lumenal spiral** (**TAILS**), within the lumina of the microtubules. The function of these TAILS is not known.

CLINICAL CONSIDERATIONS

Hydrocele is the presence of fluid accumulation between the parietal and visceral layers of the tunica vaginalis, resulting in painful swelling of the scrotum, although a sense of tenderness of the scrotum and/or testis on the affected side is frequently felt instead of pain. If hydrocele is present during infancy, it is usually a transient condition that requires no treatment, and the fluid resorbs by the end of the first year of life. In this case, the cause is congenital malformation. In older individuals, the common causes are physical trauma, infection of the testis, lymphatic obstruction, or the development of testicular tumors. Treatment depends on the causative factors and includes aspiration of the fluid, surgical removal of the tunica vaginalis, or surgical removal of the tumor.

Testicular cancer most often affects Caucasian men younger than 40 years and is the most common cancer of men between the ages of 20 and 34 years; surprisingly the incidence of this malignancy has increased in the past 40 years. The two major types are **seminomas** and **nonseminomas**. The former is composed of malignant cells that are similar to each other and resemble

spermatogonia, whereas nonseminomas are composed of malignant cells in various degrees of differentiation. The cause of testicular cancer is not known, although it is associated with cryptorchidism. Symptoms during the early stages include enlarged and most frequently painless testis with or without the presence of a tactile tumor as well as backaches and dull pain in the lower abdominal region. In later stages, the symptoms include obstruction in the urine flow, feeling of fatigue and lethargy, tumors in the abdomen, shortness of breath, and coughing. These all indicate that the malignancy is no longer restricted to the testis but has metastasized, via the lymphatic system, to the lungs, bone, liver, and the abdomen. Individuals with *nonseminomas* typically have elevated blood **human corticotrophin**, **α-fetoprotein**, and **human chorionic gonadotropin (hCG)** levels, whereas patients with *seminomas* present with normal **α-fetoprotein** and elevated **hcg** levels. Common treatment is surgical removal of the affected testis along with removal of the retroperitoneal lymph nodes followed, usually, by radiation and chemotherapy.

E. Regulation of spermatogenesis

1. **Critical testicular temperature** is 35°C (95°F) for spermatogenesis. During development, testicular arteries that arise from the aorta accompany the descending testes into the scrotum, providing each testis with a vascular supply. As these convoluted arteries approach the testes, they are surrounded by a **pampiniform plexus of veins** that dissipate the heat of the arterial blood, resulting in its temperature being reduced to 95°F.
2. **Hormonal interactions** (Fig. 18.5)

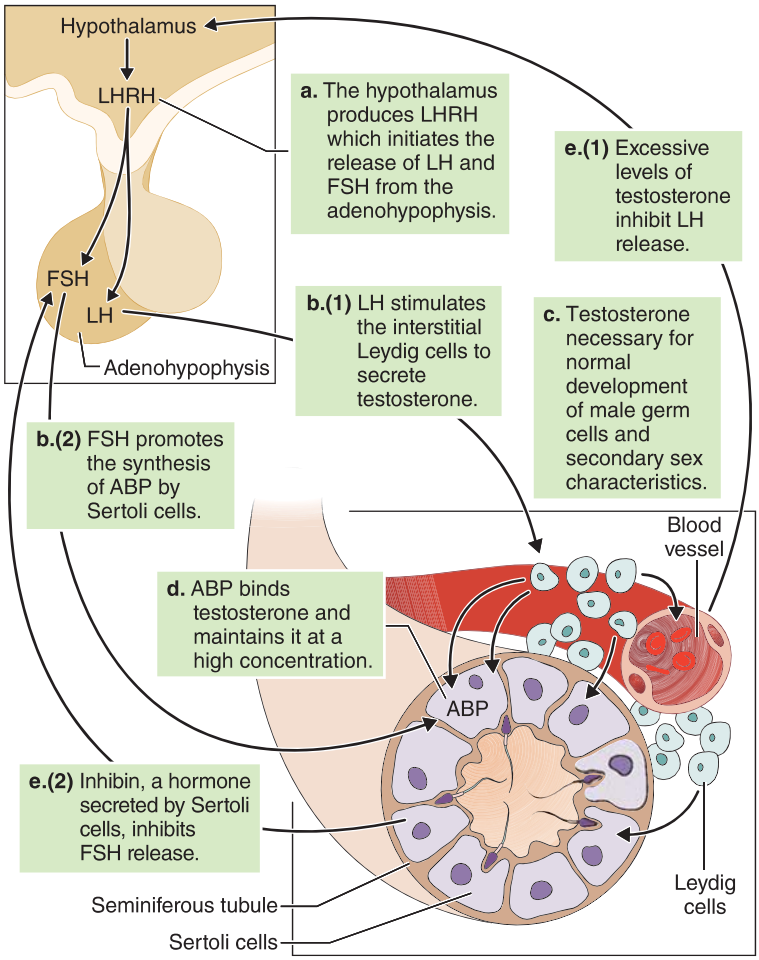


FIGURE 18.5 The hormonal control of testicular function. Note the feedback inhibition of the pituitary by testicular hormones. ABP, androgen-binding protein; FSH, follicle-stimulating hormone; LH, luteinizing hormone; LHRH, luteinizing hormone–releasing hormone.

a. **Certain neurons in the hypothalamus** produce luteinizing hormone–releasing hormone (LHRH), also known as gonadotropin-releasing hormone (GnRH). LHRH initiates the release of LH and FSH from the adenohypophysis.
b. **Stimulation of testicular hormone production** is effected by LH, which stimulates the interstitial cells of Leydig to secrete **testosterone**; and by FSH, which promotes the synthesis of **ABP** by Sertoli cells.
c. **Testosterone** is necessary for the normal development not only of male germ cells but also of secondary sex characteristics.
d. **ABP** binds testosterone to maintain it at a high concentration in the seminiferous tubule to facilitate succession of spermatogonia into spermatozoa; it can also bind estrogens, thus inhibiting spermatogenesis.
e. **Inhibition and stimulation of FSH and LH release**
   (1) Excessive levels of **testosterone** inhibit LH release.
   (2) **Inhibin**, a hormone secreted by Sertoli cells, inhibits GnRH and, thereby, FSH release from the hypophysis.
   (3) **Activin**, also secreted by Sertoli cells, stimulates the release of GnRH and, thereby, FSH release.

CLINICAL CONSIDERATIONS

Hyperthermia is a major factor that results in sterility in males. Sperm production is heat sensitive. The optimum temperature for sperm production is 35°C (95°F). Hence, the testes are housed in the scrotum as opposed to being housed within the body, where the temperature would be around 98°F. Some studies show that males who operate laptop computers situated in their laps for an hour are increasing their intrascrotal temperatures by as much as 2.8°C (5°F). Although these studies are not definitive, young males might consider limiting the use of laptop computers in their laps for extended time periods.

One of the side effects of **vitamin A deficiency** is male sterility. The testes preferentially take up **vitamin A** from the blood and convert it into retinoic acid, which binds to **retinoic acid receptors alpha** (**RARa**) of Sertoli cells, a nuclear receptor that regulates transcription during spermatogenesis and other developmental processes. Interference with the gene coding for RARa disrupts spermiogenesis by interfering with the proper alignment of the spermatozoa, preventing their release from the seminiferous tubules, and resulting in male infertility. In a recent study, an experimental nonsteroidal drug, BMS-189453, which is an RARa antagonist, given to mice orally was able to block RARa and resulted in the same type of infertility as does interfering with the gene that codes for RARa; however, shortly after the drug was discontinued, the mice regained their fertility and were able to produce normal offspring. Investigations are continuing in the development of this drug to determine whether or not it would be an effective male contraceptive.

Vasectomy is the chosen means of permanent contraception by more than 600,000 U.S. males each year. A physician may perform the procedure in the office, where an incision is made in the scrotum, and a portion of the spermatic cord is pulled out, cut, cauterized, and returned to the scrotum. Approximately 6 weeks postprocedure, semen is collected and examined to ensure that no spermatozoa are ejaculated. This procedure is nearly 100% effective. The procedure may have a few complications, but they usually dissipate after a short period of time.

III. GENITAL DUCTS (Table 18.3)

A. Intratesticular ducts

1. The continuations of the seminiferous tubules are the **tubuli recti**, short, straight tubules lined by Sertoli cells in their proximal half and lined by a **simple cuboidal epithelium** in their distal half. These cuboidal cells possess **microvilli** and some display a single **flagellum**.
2. The **rete testis** is a labyrinthine plexus of anastomosing channels within the mediastinum testis lined by a **simple cuboidal epithelium**; many of the cells possess microvilli as well as a single luminal **flagellum**.

table 18.3 Histology and Functions of the Male Genital Ducts

Duct	Epithelium	Connective Tissue	Muscle Layers	Function
Tubuli recti	Sertoli cells in proximal half; simple cuboidal epithelium in distal half	Loose	No smooth muscle	Conduct spermatozoa from seminiferous tubules to rete testis
Rete testis	Simple cuboidal epithelium	Vascular	No smooth muscle	Conduct spermatozoa from tubuli recti to ductuli efferentes
Ductuli efferentes	Regions of ciliated columnar cells alternating with nonciliated cuboidal cells	Thin, loose	Thin layer of circularly arranged smooth muscle cells	Conduct spermatozoa from rete testis to ductus epididymis
Epididymis	Pseudostratified epithelium composed of tall principal cells with stereocilia, short basal cells	Thin, loose	Layer of circularly arranged smooth muscle cells	Conduct spermatozoa from ductuli efferentes to ductus deferens
Ductus (vas) deferens	Pseudostratified stereociliated columnar epithelium	Loose, fibroelastic	Thick three-layer smooth muscle coats: inner and outer longitudinal; middle circular	Deliver spermatozoa from tail of epididymis to ejaculatory duct
Ejaculatory duct	Simple columnar epithelium	Subepithelial; thrown into folds, giving lumen irregular appearance	No smooth muscle	Deliver spermatozoa, seminal fluid to prostatic urethra at colliculus seminalis

B. Extratesticular ducts

1. Ductuli efferentes

a. Ductuli efferentes, a collection of 10 to 20 tubules leading from the rete testis to the ductus epididymis, reabsorb fluid from the semen and form the **head of the epididymis**. The ductuli efferentes begin as intratesticular ducts, leave the testicles, and their distal portions may be considered to be extratesticular ducts. They are lined by a **simple epithelium** composed of **alternating clusters** of **nonciliated cuboidal cells** and **ciliated columnar cells.** The arrangement of epithelial cells of two different heights imparts a characteristic **festooned** appearance to the luminal outline of the ductuli efferentes.

b. They possess a thin circular layer of **smooth muscle** beneath the basal lamina of the epithelium, which is responsible for peristaltic movements.

2. Ductus epididymis (Fig. 18.6)

a. Ductus epididymis, together with the ductuli efferentes, constitutes the **epididymis**. It is surrounded by **circular layers of smooth muscle** that undergo **peristaltic contractions**, which assist in conveying sperm toward the ductus deferens.

b. The ductus epididymis is lined by a **pseudostratified columnar epithelium**, which is supported by a basal lamina and contains the following two cell types:

(1) **Basal cells** are round and, morphologically, appear to be undifferentiated; they serve as precursors of the principal cells.

(2) **Principal cells**, which are columnar and possess nonmotile stereocilia (long, irregular microvilli) on their luminal surfaces, possess a large Golgi complex, RER, lysosomes, and many apical pinocytotic and coated vesicles. They function in concert with the ductuli efferentes to absorb nearly 90% of the testicular fluid.

(a) Principal cells secrete various factors that facilitate sperm maturation; however, they also produce **glycerolphosphocholine**, which inhibits **capacitation** (the process whereby a sperm becomes capable of fertilizing an oocyte). Thus, capacitation occurs only after the sperm enters the female genital tract.

3. Ductus (vas) deferens

a. The ductus deferens, which begins at the tail of the epididymis, has a **thick muscular wall** with inner and outer layers of longitudinal smooth muscle, which are separated from one another by a middle circular layer.

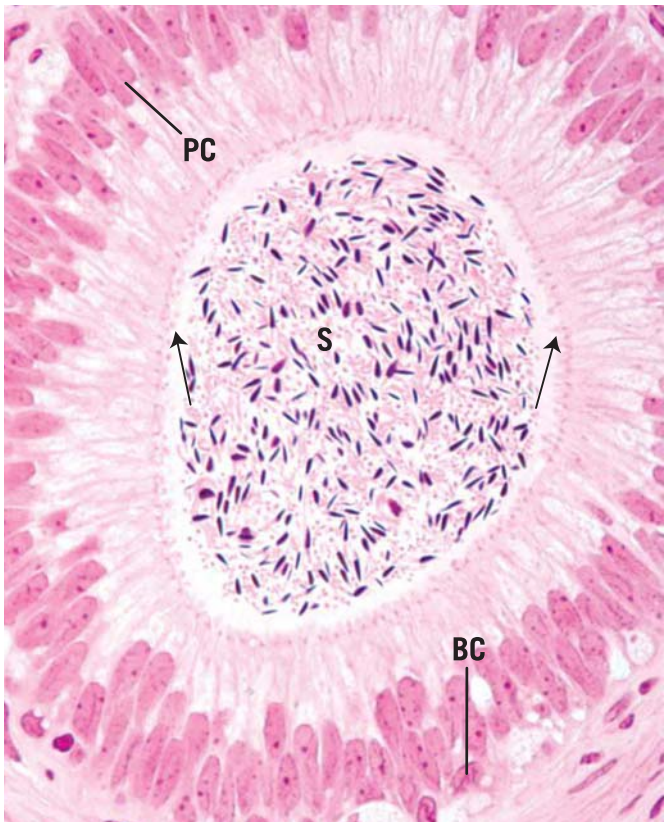


FIGURE 18.6 Light micrograph of the epididymis (×270). Observe the short basal cells (BC) and the columnar principal cells (PC) lining the lumen of the epididymis. Stereocilia (*arrows*) project into the lumen packed with spermatozoa (S).

b. It possesses a narrow, irregular lumen lined by **pseudostratified columnar epithelium** similar to that of the ductus epididymis.

4. The **ejaculatory duct**, the straight continuation of the ductus deferens beyond where it receives the duct of the seminal vesicle, lacks a muscular wall. It enters the prostate gland and terminates in a slit on the **colliculus seminalis** located in the prostatic urethra.

CLINICAL CONSIDERATIONS

A normal sperm count for a single ejaculate is approximately 50 to 100 million spermatozoa per mL. An individual with a sperm count of less than 20 million spermatozoa per mL of ejaculate is considered to be **sterile**. Between 1973 and 2011, the sperm counts of European, Australian, North American, and New Zealander men have decreased by more than 50%, whereas no such decrease was noted among African, South American, and Asian men. Although the cause of this decrease has not been ascertained, it has been suggested to be due to environmental pollutants that have a greater effect on male than on female fetuses. Additionally, adult lifestyles, such as smoking, exposure to bisphenol A, and obesity, have all been implicated in reduced sperm count.

IV. ACCESSORY GENITAL GLANDS

The accessory genital glands include the paired seminal vesicles, prostate gland, and the paired bulbourethral glands.

A. Seminal vesicles

1. The epithelium of the seminal vesicles is **pseudostratified columnar**, with a height that varies with testosterone levels; it lines the **extensively folded mucosa**. The epithelial cells house many

yellow lipochrome pigment granules and secretory granules, a large Golgi complex, many mitochondria, and abundant RER. The seminal vesicles **secrete** a yellowish, viscous fluid containing substances that **activate sperm** (e.g., fructose providing the energy source for the sperm); this fluid constitutes about 70% of the human ejaculate.

2. The **lamina propria** consists of **fibroelastic** connective tissue surrounded by an inner circular and outer longitudinal layer of smooth muscle, which, in turn, is surrounded by the **adventitia** composed of **fibroelastic** connective tissue.
3. The duct of the seminal vesicle joins the ductus deferens at its ampulla (the enlarged terminal end), thus forming the right and left ejaculatory ducts that enter the prostate gland continuing to the urethra.

B. Prostate gland (Figs. 18.7 and 18.8)

1. **Overview:** The prostate gland surrounds the urethra as it exits the urinary bladder. It consists of 30 to 50 discrete **branched tubuloacinar glands** that empty their contents via excretory ducts into the prostatic urethra. These glands are arranged in three concentric layers (**mucosal, submucosal,** and **main**) around the urethra. The entire gland is covered by a **fibroelastic capsule** that contains smooth muscle. Septa from the capsule penetrate the gland and divide it into lobes.
2. The **epithelium** of the prostate gland is **simple** or **pseudostratified columnar** and lines the individual glands that constitute the prostate. It is composed of cells that contain abundant RER, a well-developed Golgi complex, numerous lysosomes, and many secretory granules.
3. **Corpora amylacea** (see Figs. 18.7 and 18.8) are prostatic **concretions**, composed of glycoprotein, which may become calcified; their numbers increase with age.
4. The **prostate secretes** a thin, whitish fluid, a part of the semen containing proteolytic enzymes, citric acid, acid phosphatase, fibrinolysin, and lipids. The prostatic secretion serves to liquefy the coagulated semen after it is deposited in the female genital tract. Its synthesis and release are regulated by dihydrotestosterone.

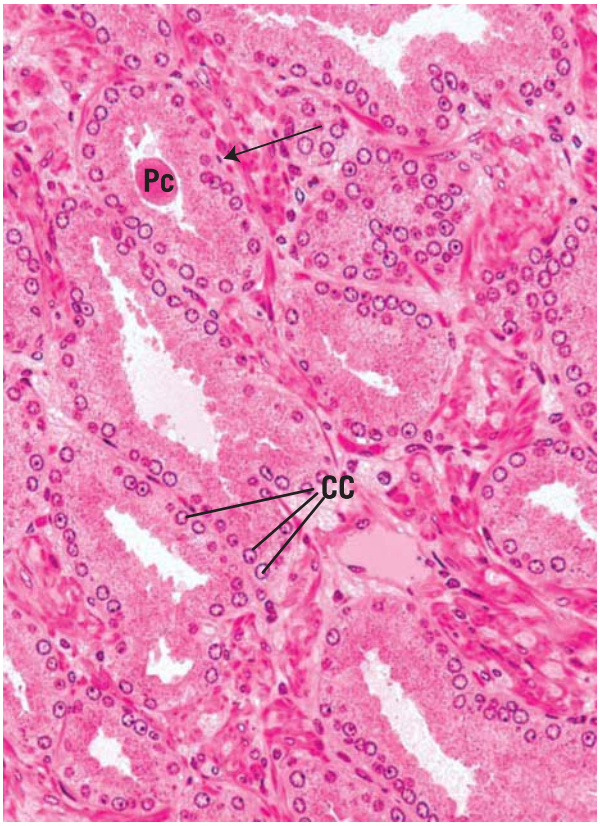


FIGURE 18.7 Light micrograph of the prostate gland (×132). Note the prostrate concretion (Pc), smooth muscle (*arrow*), and the compressed columnar cells (CC) forming the glandular parenchyma.

FIGURE 18.8 High-magnification light micrograph of a prostate gland. Observe the columnar cells (CC) and the basal cells (BC) of the parenchyma of the gland whose lumen (L) contains secretory products. The stroma (St) surrounds individual glands and forms the connective tissue framework of the prostate gland. Observe the prostatic concretion (Pc) in the lower left corner (×450).

CLINICAL CONSIDERATIONS

Benign prostatic hypertrophy (**BPH**) occurs in about 50% of men older than 50 years and in 95% of those older than 80 years. BPH can be confirmed by a digital rectal examination; however, if the diagnosis is in question, a biopsy may be necessary to rule out prostatic cancer. BPH most commonly involves only an enlargement of the **mucosal glands**. It is frequently associated with difficulty in beginning and ending urination and dribbling afterward because the urethra is partially strangulated by the enlarged prostate. BPH leads to **nocturia** (urination at night) and sensory urgency (the desire to urinate without having to void). The primary causes of BPH include arteriosclerosis, age-related hormonal alterations, inflammation of the prostate, and disturbances in the individual's metabolism. Regular digital prostate examination and blood tests for prostate-specific antigen (PSA) should be part of an annual or biannual physical examination in males older than 40 years. Complications of BPH include recurrent urinary tract infections (UTIs), formation of urinary bladder diverticula, and pressure on the prostatic portion of the urethra leading to diminished urine flow; in the worst chronic cases, this leads to acute kidney failure. Early symptoms of BPH include diminished urinary flow and inability to completely empty the bladder; later symptoms include increased frequency of urination during the day as well as at night (nocturia); partial to complete incontinence; and, eventually, blood in the urine (hematuria). Treatments of BPH include physical exercise to strengthen muscles of the pelvic floor, reduced caffeine and alcohol consumption, and decreased fluid intake. Use of certain medications, such as 5-α-reductase inhibitors (5-ARIs) to reduce the prostate size (although 5-ARIs have the unfortunate association with aggressive prostate cancers) and α-blockers that act to relax muscles of the urinary bladder, can also be part of the treatment modalities. Surgical procedures may also be employed if the noninvasive treatments are not effective. These include thermotherapy, laser therapy, and prostate resection that remove part of the prostate gland as well as more aggressive surgical procedures to remove the entire prostate.

Adenocarcinoma of the prostate gland occurs in about one-third of men older than 75 years and is the second most common form of cancer in men. The incidence and severity of the malignancy are more common in African-Americans than in Caucasians. A genetic disposition is apparent, in that, if close family members had prostate or breast cancers, the risk of prostate cancer is increased. Although lifestyle risk factors, such as a high consumption of red meat, processed meats, and dairy products as well as minimal consumption of fruits and vegetables, have been shown to have an association with prostate cancer, these links have not been proven. Most forms of prostate cancers are slow-growing and reside completely within the prostate gland, but others are more aggressive, grow faster, and spread to other regions of the body, some near the prostate, such as the urinary bladder, some at a distance from the prostate, such as bones and lymph nodes. The symptoms of prostate cancer are more evident later than in the early stages and these include problems with urination, such as difficulties in beginning micturition, weaker urine flow, dribbling prior to or after urination, blood in the urine, scrotal edema, and pain in the pelvic region and/or in bones. Prostate cancer may be detected by palpation through the rectum, where, instead of a smooth surface, dense lumps are perceived. However, a biopsy is required for positive identification of the disease. Although this cancer grows slowly, it commonly **metastasizes to bone** via the circulatory system. Cancer of the prostate is associated with an elevated **PSA** level in blood; however, it is not a definitive test, and some U.S. Task Forces have counseled against the use of PSA because of the possibility of false-positive results, leading to potentially harmful consequences to the individual. However, with that in mind, men with elevated PSA values may wish to become candidates for more aggressive diagnostic tests for the disease. Surgical removal, radiation, hormone, and chemotherapy are the usual treatments, although complications of impotence and/or incontinence may result. Importantly, men over the age of 65 years in whom prostate cancer is not aggressive (Gleason score of less than 5) and who receive no treatment but are carefully monitored by their oncologist frequently die of causes other than prostate cancer.

The **Gleason score**, ranging from 2 to 10, is a means of determining the aggressiveness of the patient's prostate cancer (based on the tissue biopsy) and suggesting the treatment modality. The two components of the Gleason score include the ***arrangement*** of the architectural differentiation of the tumor biopsy, in which increasing differentiation is assigned a higher number (range from 1 through 5), and the ***number of patterns*** evident, with the highest two patterns added together. Therefore, if the patient's biopsy shows an arrangement of 2 and the patterns show 4 and 2, then the Gleason score is $4 + 2 = 6$. A Gleason score of 2 to 4 is considered to be unlikely to metastasize, a Gleason score of 5 to 7 is mostly treatable with a good prognosis, and a Gleason score higher than 7 is most probably incurable because the tumor is very aggressive.

C. Bulbourethral (Cowper) glands are adjacent to the membranous urethra, lined by a *simple cuboidal* or *columnar epithelium* and surrounded by a *fibroelastic capsule* containing smooth and skeletal muscle. They empty their viscous, slippery secretions into the lumen of the membranous urethra to lubricate it just prior to the emission of semen.

V. URETHRA

The urethra conveys urine from the bladder to outside the body. In males, the urethra also carries semen during ejaculation. It has a **two-layered muscularis** consisting of an inner longitudinal and an outer circular layer of smooth muscle. It is surrounded at some point by an **external sphincter of skeletal muscle**, which permits its voluntary closure.

A. The male urethra is about 20 cm long and is divided into *prostatic*, *membranous*, and *cavernous* portions.

B. It is lined by *transitional epithelium* in the prostatic portion and by *pseudostratified* or *stratified columnar epithelium* in the other two portions. The **fossa navicularis**, located at the distal end of the cavernous urethra, is lined by **stratified squamous epithelium.**

C. It contains mucus-secreting *glands of Littre* in the lamina propria.

VI. PENIS

The **penis**, the male copulatory organ, is composed of three cylindrical tissues, the two **corpora cavernosa** and the single, ventrally positioned **corpus spongiosum**, whose distal end forms the glans penis. The penis is covered with skin, which at the distal end of the penis forms a double-layered fold, known as the **foreskin** that protects the glans penis. All three corpora are erectile in nature in that they possess vascular spaces that are usually empty, causing the penis to be **flaccid** until erotic stimulation—physical or imaginary—causes a change in blood flow into the vascular spaces, with a resultant enlargement and hardening of the penis, known as **erection**; in this condition, the penis is able to deliver **semen**, through the urethra, to the outside of the man's body, a process known as **ejaculation**. After ejaculation, blood flow leaves the erectile tissue's vascular spaces and the penis returns to the flaccid state. The urethra delivers not only semen to the outside but also the urine produced by the kidneys and stored in the urinary bladder.

A. Corpora cavernosa are paired masses of erectile tissue that contain *irregular vascular spaces* lined by a continuous layer of endothelial cells. These spaces, which decrease in size toward the periphery of the corpora cavernosa, are separated from each other by trabeculae of connective tissue and smooth muscle. During erection, the vascular spaces become engorged with blood as a result of **parasympathetic impulses**, which constrict arteriovenous shunts and dilate the helicine arteries, thus increasing flow to the vascular spaces of the two corpora cavernosa and the single corpus spongiosum.

B. The corpus spongiosum is a single mass of *erectile tissue* that contains vascular spaces of uniform size. It possesses **trabeculae** that contain more elastic fibers and less smooth muscle than those of the corpora cavernosa. The penile portion of the urethra passes through the length of the corpus spongiosum, opening to the exterior at the tip of the glans penis.

C. Connective tissue and skin

1. The **tunica albuginea** is a thick, fibrous connective sheath that surrounds the paired corpora cavernosa and the corpus spongiosum. The arrangement of dense collagen bundles permits extension of the penis during erection.
2. **Glans penis**, the dilated distal end of the corpus spongiosum, contains dense connective tissue and longitudinal muscle fibers. It is covered by retractable skin, the **foreskin** (whose homologue is the clitoral hood over the female clitoris, and the two are known by the collective term **prepuce**), which is lined by stratified squamous lightly keratinized epithelium.
3. **Glands of Littre** are mucus-secreting glands present throughout the length of the penile urethra.

CLINICAL CONSIDERATIONS

Studies show that **uncircumcised** males harbor anaerobic bacteria in the deep fold of the foreskin, and this microbiome increases susceptibility to human immunodeficiency virus (HIV) infection when having unprotected sex with a female who is also infected. However, circumcised males had a lower risk of acquiring HIV infection under similar conditions of unprotected sex with HIV-infected females. The reason for this differential may be that the presence of anaerobes induces an inflammatory response, which may provide an easier access of the HIV to the circulatory system.

UTI accompanied by fever is almost 10 times more common in infants under 3 months of age who are uncircumcised (20.1%) than those who have been circumcised (2.4%).

Possible **complications with circumcision** may occur soon after the procedure, such as wound infection, bleeding, and UTI, whereas later occurring problems include adhesions at the surgical site and stenosis of the urinary meatus. More serious problems, such as glans amputation, have also been reported.

Review Test

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A 55-year-old man complains of difficulty in urinating and having a reduced urinary flow. He also has an elevated PSA level, along with palpable hard nodules on the prostate. What is the possible diagnosis?

(A) Benign prostatic hyperplasia
(B) Adenocarcinoma of the prostate
(C) Prostatic concretions
(D) Initiation of impotence
(E) Incontinence

2. A 33-year-old man detected a swelling in his scrotum. Careful palpation did not reveal whether the swelling was associated with his testis. His physician ordered blood tests and determined that he had increased levels of hCG in his blood. What is the probable diagnosis?

(A) Benign lump
(B) Hematocele
(C) Cryptorchidism
(D) Testicular cancer
(E) Hydrocele

3. A 2-month-old baby is seen by his pediatrician because his parents noted that the baby exhibits tenderness on the left side of his scrotum when being cleaned after a diaper change. Upon examination, the pediatrician notes a slight swelling of the scrotum on the left side, indicating the presence of a hydrocele. What treatment should the pediatrician propose?

(A) Watch and wait
(B) Fluid aspiration
(C) Antibiotic therapy
(D) Removal of the tunica vaginalis
(E) Removal of the left testis

4. A 23-year-old man and his wife were complaining to their family physician about their problem with the wife becoming pregnant. The woman is an accountant working in an office of a large accounting firm, and the husband is a programmer working from home on his couch with his laptop computer on his lap, designing gaming software. The clinical tests showed that the wife should have no problems getting pregnant; however, the husband's viable sperm count was lower than it should have been, but all other clinical tests were normal. What was the most probable reason for his depressed sperm count?

(A) Hypothermia
(B) Genetic predisposition
(C) Cryptorchidism
(D) Hyperthermia
(E) BPH

5. The deficiency of which vitamin has been associated with male infertility?

(A) A
(B) B_1
(C) B_2
(D) B_3
(E) B_9

6. Lower than what sperm count value is considered sterile?

(A) 100 million spermatozoa per mL
(B) 80 million spermatozoa per mL
(C) 60 million spermatozoa per mL
(D) 40 million spermatozoa per mL
(E) 20 million spermatozoa per mL

7. A male patient was told by his urologist that his Gleason score is 8. What is the diagnosis for this patient?

(A) BPH
(B) Testicular cancer
(C) Prostate cancer
(D) Urinary bladder cancer
(E) Hydrocele

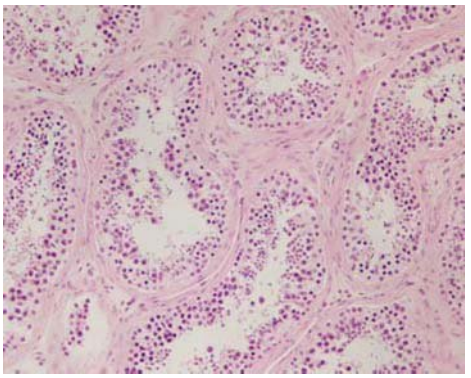
8. Which structure conveys spermatozoa from the seminiferous tubules to the rete testis?

(A) Ductus epididymis
(B) Tubuli recti
(C) Ductuli efferentes
(D) Ductus deferens
(E) Ejaculatory duct

9. What is one of the functions of the Sertoli cells?

(A) Secretion of FSH
(B) Secretion of testosterone
(C) Secretion of ABP
(D) Secretion of LH
(E) Secretion of ABP

Question 10 is based on the photomicrograph below:



10. This is a photomicrograph of a healthy area of a biopsy of a malignancy. What is the diagnosis?

(A) Testicular cancer
(B) Urinary bladder cancer
(C) Prostate cancer
(D) Penile cancer
(E) Cancer of the vas deferens

Answers and Explanations

1. **B.** Although some of the symptoms are characteristic of BPH, rectal palpation indicating hard nodules, along with an elevated PSA level, indicates probable prostatic adenocarcinoma.
2. **D.** Palpable swellings in the scrotum should be seen by a physician, especially in men younger than 40 years. Elevated blood serum levels of hCG and α-fetoprotein are usually associated with testicular cancer.
3. **A.** Hydrocele is the presence of fluid accumulation between the parietal and visceral layers of the tunica vaginalis, resulting in painful swelling of the scrotum. Frequently, instead of pain, a sense of tenderness of the scrotum and/or testis is felt on the affected side. If hydrocele is present during infancy, it is usually a transient condition that requires no treatment, and the fluid resorbs by the end of the first year of life; therefore watch and wait is the correct answer.
4. **D.** Hyperthermia is a major factor that results in sterility in males. Sperm production is heat sensitive. The optimum temperature for sperm production is 93°F. Hence, the testes are housed in the scrotum as opposed to being housed within the body, where the temperature would be around 98°F. Reportedly, males who operate laptop computers situated in their laps for an hour are increasing their intrascrotal temperatures by as much as 2.8°C. Although these studies are not definitive, young males should consider limiting the use of laptop computers in their laps for extended time periods.
5. **A.** For decades, vitamin A deficiency has been known to result in male sterility. The testes preferentially take up **vitamin A** from the blood and convert it to retinoic acid, which binds to **RARa** of Sertoli cells, a nuclear receptor that regulates transcription during spermatogenesis and other developmental processes.
6. **E.** A normal sperm count for a single ejaculate is approximately 50 to 100 million spermatozoa per mL. An individual with a sperm count of less than 20 million spermatozoa per mL of ejaculate is considered to be sterile.
7. **C.** The Gleason score, ranging from 2 to 10, is a means of determining the aggressiveness of the patient's prostate cancer (based on the tissue biopsy) and suggesting the treatment modality. A Gleason score of 5 to 7 is mostly treatable with a good prognosis, whereas a Gleason score higher than 7 is most probably incurable because the tumor is very aggressive.
8. **B.** The seminiferous tubules are connected to the rete testis by the tubuli recti.
9. **C.** Sertoli cells have many functions, including the synthesis of ABP. Testosterone is secreted by the interstitial cells of Leydig, whereas FSH and LH (also known as interstitial cell–stimulating hormone) are secreted by the pituitary gland.
10. **A.** The photomicrograph is of the testis; therefore, the patient is diagnosed with testicular cancer.

chapter 19

Special Senses

I. OVERVIEW—SPECIAL SENSE RECEPTORS

A. Special sense receptors **are responsible for the five special senses: *taste, smell, vision, hearing,* and *feeling* (which includes touch, pressure, temperature, pain, and proprioception).** The sense of smell is described in Chapter 13, and the sense of taste is described in Chapter 14. The remaining special senses are described here.

B. Function. Special sense receptors **transduce stimuli from the environment into electrical impulses.**

II. SPECIALIZED DIFFUSE RECEPTORS (Fig. 19.1)

A. Sensory receptors ***may be categorized into three groups*: exteroreceptors, *which access information from the outside environment*; proprioceptors, *which access information from muscles, tendons, and joint structures*; *and* interoceptors, *which access information from within the internal environment*.** The type of information received is also a manner of classification of receptors: **Mechanoreceptors** are activated as the receptor or tissue in which the receptor is located physically is deformed in some manner. **Thermoreceptors** are activated by either heat or cold. **Nociceptors**, also known as pain receptors, are activated by stimuli that are painful such as extreme temperatures that are hot or cold enough to cause damage to the tissues, pressure, or touch that are intense enough to cause damage to the tissues.

1. Specialized diffuse receptors, **dendritic nerve endings** in the skin, fascia, muscles, joints, and tendons, respond to stimuli related to **deep touch**, **pressure**, **temperature**, **pain**, and **proprioception**.
2. These receptors are specialized to receive only **one** type of sensory stimulus, although they will respond to other types of stimuli provided that the stimulus is sufficiently intense.
3. They are divided morphologically into **free nerve terminals** and **encapsulated nerve endings**, which are ensheathed in a connective tissue capsule.

B. Touch and pressure receptors **include Pacinian corpuscles, Ruffini endings, Meissner corpuscles, free nerve endings, and Krause end bulbs.**

1. **Pacinian corpuscles**, large ellipsoid **encapsulated** receptors in the dermis and hypodermis and in the connective tissue of the mesenteries and joints, are especially abundant in the digits and breasts.
   a. Composed of a **multilayer capsule** consisting of fibroblasts and collagen and bathed in tissue fluid, Pacinian corpuscles **often** resemble a sliced onion in histologic sections. The capsule surrounds an **inner unmyelinated nerve terminal** and perceives **pressure**, **touch**, and **vibration**.
2. **Ruffini endings**, **encapsulated** receptors in the dermis and joints, are composed of groups of **branched terminals** from myelinated nerve fibers and are surrounded by a thin connective tissue capsule. They function in **pressure**, **stretching**, and **touch** reception.

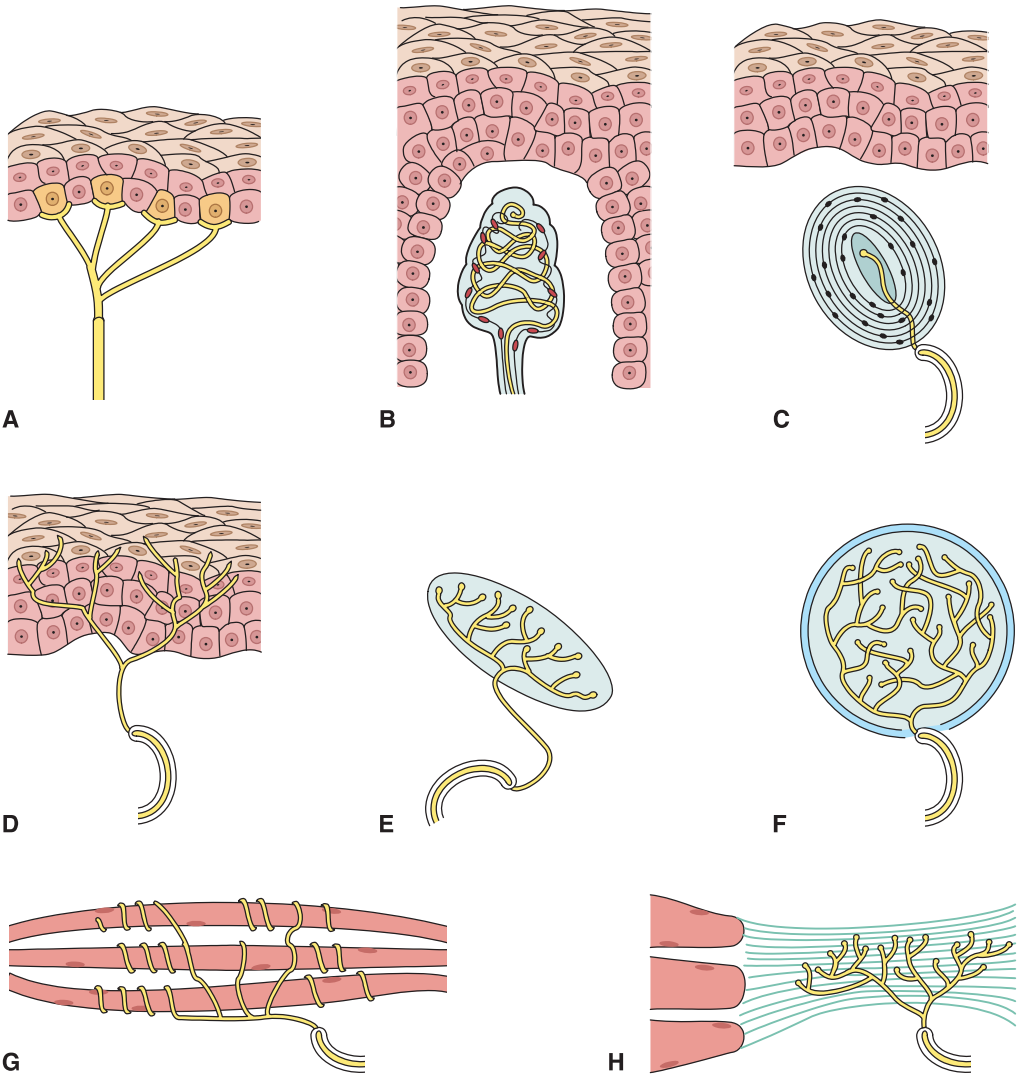


FIGURE 19.1. Various types of specialized receptors. **A.** Merkel disc. **B.** Meissner corpuscle. **C.** Pacinian corpuscle. **D.** Free nerve endings, nociceptors, and thermoreceptors. **E.** Ruffini corpuscle. **F.** Krause end bulb. **G.** Neuromuscular spindle. **H.** Golgi tendon organ.

3. **Meissner corpuscles**, ellipsoid, **encapsulated** receptors in the dermal papillae of thick skin, eyelids, lips, and nipples, possess a connective tissue capsule that envelops the nerve terminal and its associated Schwann cell. Meissner corpuscles function in **fine touch** perception.
4. **Free nerve endings**, **unencapsulated**, **unmyelinated** terminations in the skin in longitudinal and circular arrays around most of the hair follicles, function in **touch** perception.
5. **Krause end bulbs** are encapsulated receptors located in the dermis, oral cavity, peritoneum, conjunctiva, genital regions, connective tissues, nasal cavity, and joints. They were once thought to be cold receptors, but their function is currently unknown.

C. Temperature and pain receptors

1. **Cold receptors** respond to temperatures **below 25°C to 30°C**.
2. **Heat receptors** respond to temperatures **above 40°C to 42°C**.
3. **Nociceptors** are sensitive to **pain stimuli** from mechanical stress, extremes in temperature, or the presence of certain cytokines. When a stimulus is sufficiently strong to overload the normal

receptor, that stimulus may trigger pain sensations by activating the nociceptors. They are delicate myelinated fibers that lose their myelin before entering the epidermis.

D. Proprioceptive receptors are of two types, *muscle spindles* and *Golgi tendon organs* (both are described in Chapter 7).

III. SENSE OF SIGHT—EYE (Fig. 19.2)

A. Overview

1. The eyes, housed in the bony orbits, are the photosensitive organs responsible for vision. Each eye is composed of three tunics: the **tunica fibrosa** (outer layer), **tunica vasculosa** (middle layer), and **retina**, and receives **light** through the **cornea**. The light is focused by the **lens** on the **retina**, which contains specialized cells that encode the various patterns of the image for transmission to the brain via the **optic nerve**.
2. The eye possesses **intrinsic muscles** that adjust the aperture of the iris and alter the lens diameter, permitting **accommodation** for close vision as well as **extrinsic muscles**, attached to the external aspect of the eyeball, which move both eyes in a coordinated manner to perceive the desired visual fields.
3. The anterior surface of the **eyeball**, covered by the protective upper and lower eyelids, is continually moistened with **lacrimal fluid** (**tears**) secreted by the **lacrimal gland**.

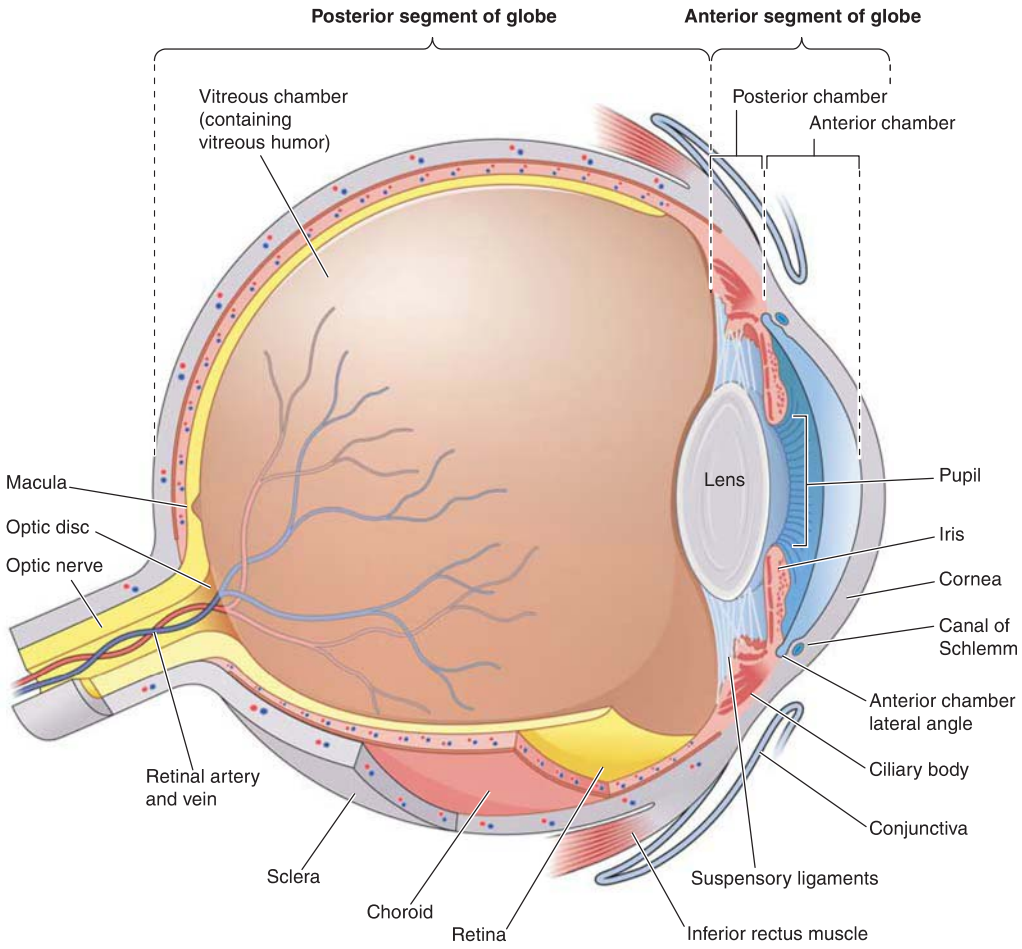


FIGURE 19.2. Anatomy of the eyeball. (Adapted with permission from McConnell TH. *The Nature of Disease*. Baltimore, MD: Lippincott Williams & Wilkins; 2007:680.)

B. Tunica fibrosa (see Fig. 19.2)

1. The outermost tunica fibrosa is composed of the sclera and the cornea. The **sclera** (white of the eye) is an **opaque**, relatively avascular fibrous connective tissue layer that covers the posterior five-sixths of the eyeball. The extrinsic ocular muscles insert into the sclera.
2. The **cornea** is the **transparent**, highly innervated **avascular** anterior one-sixth of the tunica fibrosa. It joins the sclera in a region called the **limbus**. The cornea is composed of five layers.
   - **a. Corneal epithelium**, a **stratified squamous nonkeratinized epithelium**, lines the **anterior aspect** of the cornea and is continuous with the **conjunctiva** (a mucous membrane covering the anterior sclera and lining the internal surface of the eyelids). It is highly innervated with free nerve endings.
     - **(1)** It possesses **microvilli** in its superficial layer, which trap moisture, protecting the cornea from dehydration.
   - **b.** The **Bowman membrane** is a homogeneous **noncellular** layer that provides form, stability, and strength to the cornea. The basal layer of the corneal epithelium is attached to the Bowman membrane via hemidesmosomes.
   - **c. Corneal stroma** is the thickest corneal layer. It is composed of about five layers of both **type I** and **V collagen fibers** lying parallel to each other within each row and at oblique angles to each other in adjoining layers, thus forming a lattice. These collagen fibers are embedded in a ground substance composed mostly of chondroitin sulfate and keratan sulfate. A few fibroblasts are located between the lamina of collagen fibers.
     - **(1)** The stroma has tunnels in the region of the limbus that are lined by **endothelium**, forming the **canal of Schlemm** (see Fig. 19.2). This canal drains fluid (aqueous humor) from the anterior chamber of the eye into the venous system.
   - **d.** The **Descemet membrane** is a thick (5–10 μm) basal lamina interposed between the endothelium and the connective tissue stroma of the cornea.
   - **e. Corneal endothelium**, a **simple squamous epithelium** with cells that exhibit numerous **pinocytic vesicles**, lines the **posterior aspect** of the cornea beneath the Descemet membrane where it separates the cornea from the aqueous humor in the anterior chamber of the eye. The cells of the corneal endothelium **resorb fluid** from the stroma, thus contributing to the transparency of the cornea, facilitating refraction of light.

CLINICAL CONSIDERATIONS

Because the **cornea** is without a blood supply and lymphatics, the cornea may be transplanted without eliciting an immune response that would result in tissue rejection. Thus, it is one of the most frequently donated tissues.

In the **corneal reflex** (**blink response**) test, a wisp of cotton that has touched the cornea will cause the patient to blink. The blink is a test of the integrity of the ophthalmic division of the trigeminal nerve (cranial nerve [CN] V).

Delivery of ocular medicines for conditions such as dry eyes, myopia, glaucoma is done by the use of an eyedropper. However, a variety of problems, such as blinking, contamination, and overflow of the medication, result in inconsistent doses being applied. In fact, the dropper is designed to deliver a drop that is about 40 μL, an excess of three times the required dose to compensate for the delivery method. Recent investigations using modifications of the piezo-print technology can deliver the correct dose in a 7 μL droplet that is applied within 80 milliseconds, so that the patient does not have the time to blink during the delivery of the fluid. Moreover, the fluid is delivered to the cornea, the region of the eyeball that absorbs almost all of the medication, rather than to the sclera, which is much less able to absorb it. The delivery method is in the process of clinical trials.

The almost universal acceptance of **contact lenses** in the United States has led the Centers for Disease Control to initiate studies of risky behaviors of individuals who wear them. Almost 41 million Americans wear contacts, and 93% of them wear soft lenses; 99% of the surveyed group have admitted to committing at least one hazardous behavior. The most common of these behaviors were taking a nap while wearing the lenses (87%), showering with the lenses in the eyes, swimming while wearing the lenses (61%), adding fresh cleaning solution to the old solution (55%), not replacing the lenses at suggested intervals (50%), sleeping all night long while wearing the lenses (50%), using tap water instead of cleaning solution to rinse the contact lenses (35%), continuing to wear contacts during eye infection (30%), and storing the lenses in tap water rather than in cleaning solution (17%). The use of tap water is the riskiest of these behaviors because transferring microbes from the water into the eye causes eye infections.

C. **The tunica vasculosa (*uvea*, the middle tunic) is composed of three parts: choroid, ciliary body, and iris (see Fig. 19.2).**

1. **Choroid**, the **highly vascular**, **pigmented layer** of the eye, is loosely attached to the tunica fibrosa; its loose connective tissue contains many **melanocytes**.
   a. The deepest layer of the choroid, the **Bruch membrane**, extends from the ora serrata to the optic disc and separates the choriocapillary layer from the pigment epithelium. It is composed of two thin layers of collagen fibers with an intervening layer of elastic fibers. Both layers of collagen fibers are covered by basal laminae.
   b. The **choriocapillary layer** contains the blood capillaries derived from the choroid stroma that supply the retina.
2. The **ciliary body**, the wedge-shaped anterior expansion of the choroid, completely encircles the lens and separates the ora serrata from the iris. It is lined on its inner surface by two layers of cells: an **outer pigmented columnar epithelium** rich in melanin and an **inner nonpigmented simple columnar** epithelium.
   a. The **ciliary processes** are radially arranged extensions (about 70) of the ciliary body. They have a connective tissue core containing many **fenestrated capillaries** and are covered by two epithelial layers. The **nonpigmented inner layer** transports components from the plasma filtrate in the posterior chamber and thus forms the **aqueous humor**, which flows to the anterior chamber via the pupillary aperture (see Fig. 19.2). The ciliary processes possess **suspensory ligaments** (zonulae) that arise from the processes and insert into the capsule of the lens, serving to anchor it in place.
   b. The **ciliary muscle**, innervated via **parasympathetic fibers** of the **oculomotor nerve** (CN III), is attached to the sclera and ciliary body in such a manner that its contractions stretch the ciliary body and release tension on the suspensory ligament and lens. Ciliary muscle contraction permits the lens to become more convex, allowing the eye to focus on nearby objects (**accommodation**). With advancing age, the lens loses its elasticity, thereby gradually losing the ability to accommodate.
3. The **iris**, the most anterior extension of the choroid, separating the anterior and posterior chambers of the eyeball (see Fig. 19.2), incompletely covers the anterior surface of the lens, forming an aperture called the **pupil** that is continually adjusted by intrinsic pupillary muscles.
   a. It is covered by an incomplete layer of pigmented cells and fibroblasts on its anterior surface and has a wall composed of loose vascular connective tissue containing melanocytes and fibroblasts. On its deep surface, it is covered by a two-layered epithelium **possessing** pigmented cells that block light from entering the interior of the eye except via the pupil. Eye color is blue if only a few melanocytes are present. Increasing amounts of pigment manufacturing melanocytes impart darker colors to the eye.
   b. The **dilator pupillae muscle**, a **smooth muscle** with fibers that radiate from the periphery of the iris toward the pupil, contracts upon stimulation by **sympathetic** nerve fibers, **dilating the pupil**.
   c. The **sphincter pupillae muscle**, a **smooth muscle** arranged in concentric rings around the pupillary orifice, contracts upon stimulation by **parasympathetic** nerve fibers of the oculomotor nerve (CN III), **constricting the pupil**.

D. **Refractive media**

1. **Aqueous humor**, a **plasma-like fluid** in the anterior compartment of the eye, is **formed by epithelial cells lining the ciliary processes**. It is constantly secreted into the posterior chamber of the

CLINICAL CONSIDERATIONS

Glaucoma, the leading cause of blindness in African-Americans in the United States; worldwide it is the second leading cause of blindness after cataracts and is a condition of abnormally **high intraocular pressure**. It is caused by obstructions that prevent drainage of aqueous humor from the eye via the canal of Schlemm, resulting in buildup of pressure. An age-related condition, glaucoma affects about 1 in 10 persons 80 years of age and older.

Chronic glaucoma (**primary open-angle glaucoma**), the most common form of glaucoma in the United States (over 90% of glaucoma sufferers), may be associated with few symptoms except for a gradual loss of peripheral vision. However, usually, this condition can be controlled with medication in the form of eye drops.

Closed-angle glaucoma (less than 10% of glaucoma sufferers in the United States) is associated with the abrupt appearance of pain in the affected eye, poor vision, inflamed sclera, a somewhat dilated pupil that does not respond to light, and the presence of haloes when looking at bright lights, all because of a sudden increase in pressure within the eyeball. This condition must be treated soon after the appearance of the symptoms, otherwise permanent blindness will follow in the affected eye.

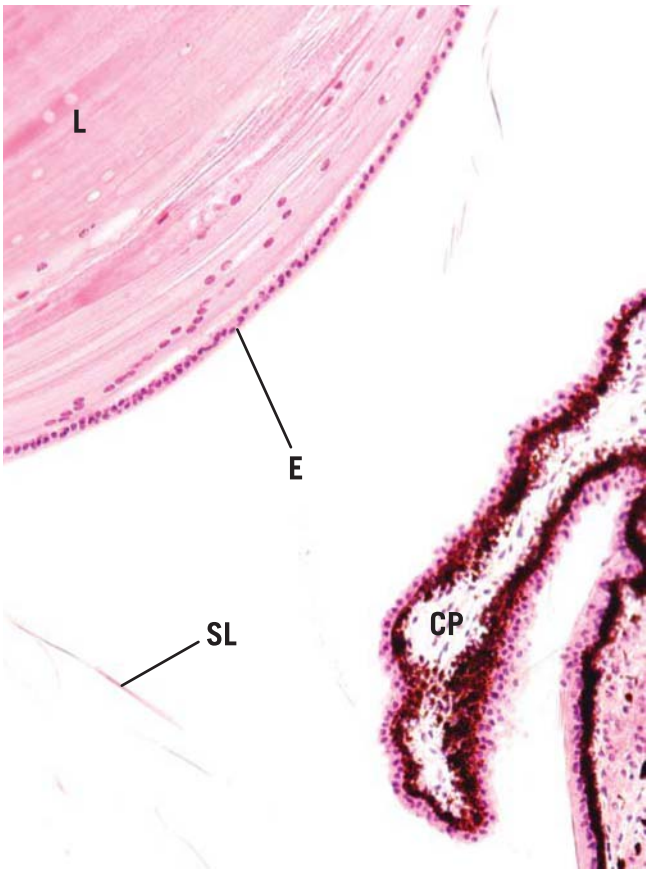


FIGURE 19.3. Light micrograph of the lens of the eye (×132). Observe the lens (L), epithelium (E), suspensory ligament (SL) of the lens, and the ciliary process (CP).

eye and then flows into the anterior chamber of the eye via the pupillary aperture; from there it enters the venous system via the canal of Schlemm (see Fig. 19.2).

2. The **lens** is a biconvex **transparent** flexible structure composed of the lens capsule, subcapsular epithelium, and lens fibers (Fig. 19.3).
   a. The **lens capsule** is a thick basal lamina that envelops the entire lens epithelium.
   b. The **subcapsular epithelium** (on the anterior and lateral lens surfaces only) is composed of a single layer of cuboidal cells that communicate with each other via **gap junctions** and interdigitate with lens fibers.
   c. **Lens fibers** represent highly differentiated, elongated cells that when mature **lack** both nuclei and organelles. Lens fibers are filled with a group of proteins called **crystallins**.
   d. The **suspensory ligament** stretches between the lens and the ciliary body, keeping tension on the lens and **enabling it to focus on distant objects**.
3. The **vitreous body** is a **refractile gel** composed mainly of water, collagen, and hyaluronic acid. This gel fills the interior of the globe posterior to the lens (see Fig. 19.2).

CLINICAL CONSIDERATIONS

A **cataract**, an **opacity of the lens** resulting from the accumulation of pigment or other substances in the lens fibers that scatter the light entering the lens, prevents sharp focusing of the light on the retina. Cataracts are often associated with **aging** and, if untreated, may lead to a gradual loss of vision. When the opacity becomes severe, an ophthalmologist may remove and replace the affected lens with a man-made lens, restoring clear vision.

Presbyopia is the inability of the eye to focus on close objects (accommodation). This is usually associated with aging and decreasing elasticity of the lens, which prevents it from assuming a spherical shape. This condition can usually be corrected with eyeglasses.

Eye floaters (vitreous opacities) are age-related changes in which the gel-like vitreous body becomes more liquid and causes debris within it to clump. As light passes through the vitreous body,

the debris forms shadows on the retina that appear as black spots, streaks, strings, spider webs, etc., which move about in the visual fields. These eye floaters may become an annoyance; however, most people learn to disregard them. Usually, the floaters resolve in a few weeks or so. When eye floaters are accompanied by bright flashes of light or fuzzy vision, an ophthalmologist should be consulted as this may indicate a tear in the retina.

E. The retina (Figs. 19.4 and 19.5 and Table 19.1), the innermost of the three tunicae of the eye, is composed of two layers: a photosensitive layer containing rods and cones and several interneurons, and a nonsensitive pigmented layer housing melanin-producing cells. It is interposed between the choroid and the vitreous humor and is responsible for **photoreception**. The photosensitive (visual) portion of the retina ends at the **ora serrata**, whereas the nonsensitive (pigmented) portion continues anteriorly to cover the **ciliary body** and the **posterior surface of the iris**. The retinal layer has a shallow depression in its posterior wall that contains only cones; this avascular region, called the **fovea centralis**, has a central region called the **macula**, which exhibits the greatest visual acuity (see Fig. 19.2). The retina displays **10 distinct layers** (see Table 19.1); later in the chapter, they are discussed in order from the outermost to the innermost. Only some of these 10 cell layers are composed of neurons that receive, integrate, and relay or transmit impulses to the brain for processing. These include photoreceptor rods and cones, bipolar cells, and ganglion cells. Cells of the remaining layers function in supporting the architecture of the retina.

1. The **retinal pigment epithelium** is a layer of **columnar cells** firmly attached to the **Bruch membrane**.
   a. Retinal pigment epithelial cells have **junctional complexes**; their **basal invaginations** contain mitochondria, suggesting the involvement of these cells in ion transport. They

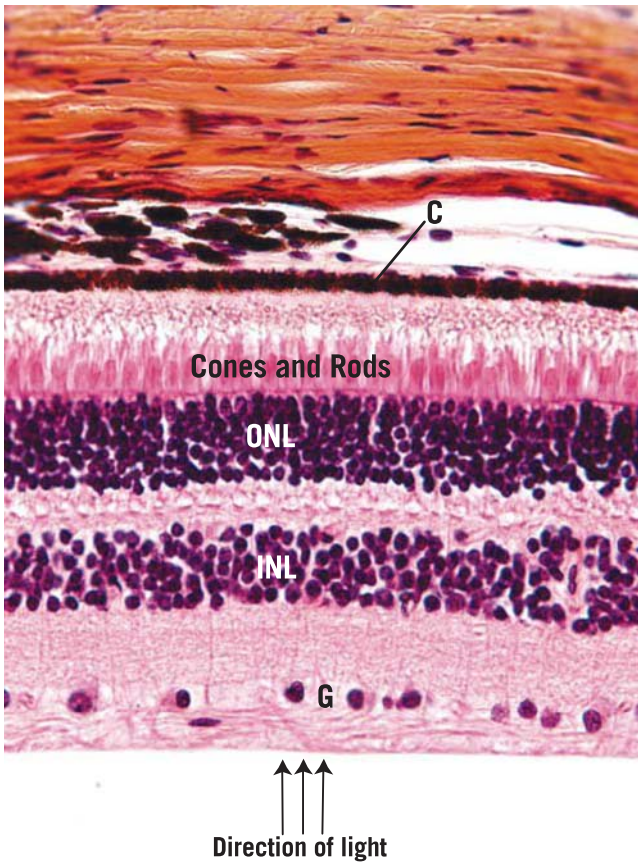


FIGURE 19.4. Light micrograph of the retina (×132). Observe the choroids above to the pigmented epithelial layer (C), the rods and cones, outer nuclear layer (ONL), the inner nuclear layer (INL), and the ganglion layer (G).

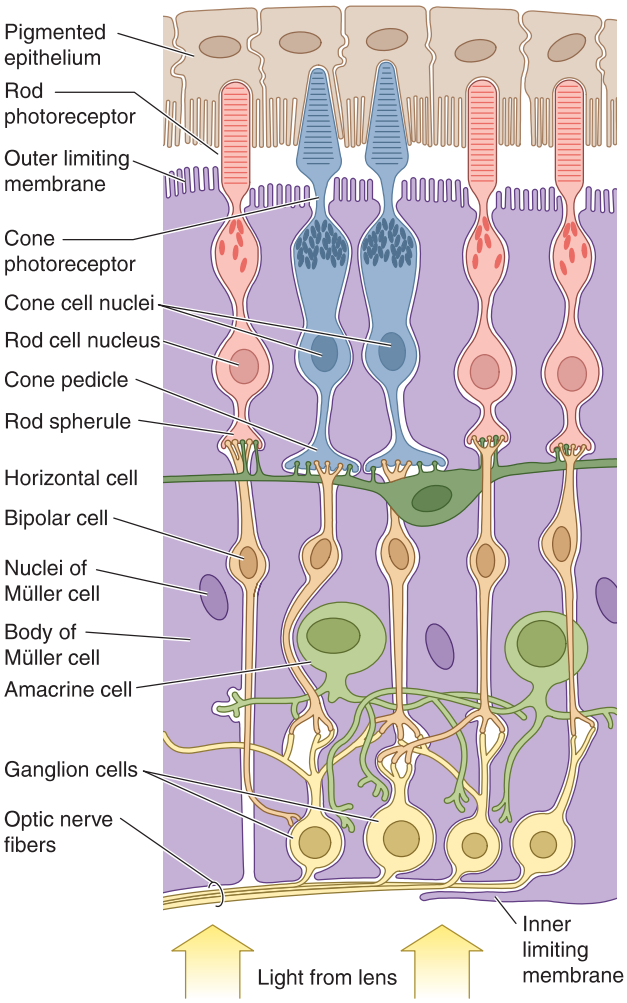


FIGURE 19.5. The layers of the retina. (Adapted with permission from Gartner LP. *Textbook of Histology*. 4th ed. Philadelphia, PA: Elsevier; 2017:593.)

table 19.1 Layers of the Retina (from Outer to Inner, Adjacent the Vitreous Humor)

Layer #	Name	Components
1	Retinal pigment epithelium	Pigmented cells
2	Layer of rods and cones	Outer and inner segments of rods and cones
3	External limiting membrane	Zonulae adherentes of apical aspects of Müller cells with rods and cones
4	Outer nuclear layer	Nuclear regions of rods and cones
5	Outer plexiform layer	Region of synapses with rods, cones, horizontal cells, and bipolar cells
6	Inner nuclear layer	Soma of horizontal, bipolar, and amacrine cells
7	Inner plexiform layer	Region of synapses with bipolar, amacrine, and ganglion cells
8	Ganglion cell layer	Cell bodies of ganglion cells
9	Optic nerve fiber layer	Unmyelinated axons of ganglion cells that form the optic nerve
10	Inner limiting membrane	Basal portions of Müller cells and their basement membranes

contain smooth endoplasmic reticulum and many **melanin granules** located apically in cellular processes. They form **pigment-filled microvillus processes** that invest the tips of the rods and cones.

b. Retinal pigment epithelial cells **esterify vitamin A** (used in the formation of visual pigment by rods and cones); **phagocytose** the shed tips of the outer segments of rods; **synthesize melanin**, which absorbs light after the rods and cones have been stimulated; and serve as the blood–retinal barrier.

2. The **photoreceptor layer** consists of neurons (photoreceptor cells) called rods and cones (see Fig. 19.5).

a. Rods (sensitive to light of low intensity) possess four regions: outer and inner segments, a nuclear region, and a synaptic region. They may synapse with bipolar cells, giving rise to **summation**. They possess an **incomplete cilium** terminating in a basal body within the inner segment.

(1) Outer segments of rods consist mainly of hundreds of **flattened membranous discs** that contain **rhodopsin**, the visual pigment located in the discs of rods and discs of cones. They eventually shed their discs, which are subsequently phagocytosed by the pigment epithelial cells.

(2) Inner segments of rods possess mitochondria, glycogen, polyribosomes, and proteins, which migrate to the outer segments to be incorporated into the membranous discs.

(3) Photoreception by rods is initiated by the interaction of **light** with **rhodopsin** (**visual purple**), which is composed of the integral membrane protein **opsin** bound to **retinal**, the aldehyde form of vitamin A.

(a) When the retinal moiety of rhodopsin **absorbs light** in the visible range, retinal dissociates from opsin. This reaction, called **bleaching**, eventually closes the Na^+ channels, thus permitting diffusion of bound **Ca^{2+} ions** into the cytoplasm of the outer segment of a rod cell.

(b) Excess **Ca^{2+}** acts to **hyperpolarize** the cell because Na^+ is prevented from entering the cell.

(c) Ionic alterations in the rod generate electrical activity, which is relayed to other rods via gap junctions.

(d) Dissociated retinal and opsin **reassemble** by an active process in which Müller cells and pigment epithelial cells also participate.

(e) Ca^{2+} is recaptured by the membranous discs, leading to reopening of the Na^+ channels and **reestablishment** of the normal resting membrane potential.

b. Cones (sensitive to light of high intensity) (see Fig. 19.5) are **much less numerous than rods** but produce **greater visual acuity** than do rods; thus, the macula is populated only by cones. They are generally similar in structure to rods and mediate photoreception in the same way, with the following exceptions:

(1) The membranous discs in the outer segments of cones are invaginations of the plasma membrane, whereas in rods they are not.

(2) The proteins synthesized in the inner segments of cones are passed to the entire outer segment, whereas, in rods, they are added only to newly forming discs.

(3) Cones possess **iodopsin** in their discs. The amount of this photopigment varies in different cones, making them differentially sensitive to red, green, or blue light.

(4) Each cone synapses with a **single** bipolar neuron, whereas each rod may synapse with several bipolar neurons.

CLINICAL CONSIDERATIONS

Age-related macular degeneration (**AMD**) is a disease of the retina located in the central region of the macula, hence affecting central vision. As its name implies, it is a disease of aging, occurring usually after the age of 50 years. The two forms are dry and wet AMD.

In **dry macular degeneration**, the most common form, the central vision is affected so that objects become very blurred. This is caused by cellular debris (drusen) that appears as yellow spots deposited between the choroids and the retina. Recent investigations of injecting embryonic stem cells that were induced to differentiate into retinal pigment epithelial cells between the retina and

the sclera demonstrated that the injected cells survived and did not cause any deleterious effects. Instead, these transformed cells were able to ameliorate the vision problems for some of the patients involved. Clinical trials using transformed embryonic stem cell therapy are currently being conducted.

Wet macular degeneration, the most severe form, results when small blood vessels, formed between the choroid and the retina, leak into this space causing the retina to die, and, as a result, a blind spot forms in the center of the visual field. Wet macular degeneration exhibits a quick onset with a small blind spot that may quickly progress to a larger blind spot. Although an AMD patient may be unable to recognize a face in the center of vision, interestingly, the peripheral vision is unaffected by macular degeneration. Although a cure has not been found, certain vitamins and high doses of antioxidants and zinc may be of some benefit for dry AMD, whereas laser surgery and injections of antiangiogenesis drugs are used to manage wet AMD.

Retinal detachment occurs when the neural and pigmented layers separate from each other, for example, as a result of a sudden hard jolt. This condition can sometimes be treated successfully by laser surgery. But, extensive separation requires cryosurgery to produce successful adhesion of the two layers. If retinal detachment is left untreated, blindness may occur, and, often even with treatment, the rods and cones die, leaving blind spots in the visual field.

3. The **external limiting membrane** is not a true membrane but an area where **zonulae adherentes** (belt desmosomes) are located between the photoreceptor cells and the retinal Müller cells (glial cells). It also contains microvilli that project from the Müller cells.
4. The **outer nuclear layer** consists primarily of the **nuclei of the rods and cones**.
5. The **outer plexiform layer** contains **axodendritic synapses** between the axons of photoreceptor cells and the dendrites of bipolar and horizontal cells. It displays **synaptic ribbons** within the rod and cone cells at synaptic sites.
6. The **inner nuclear layer** contains the **cell bodies of bipolar neurons**, horizontal cells, amacrine cells, and the nuclei of Müller cells.
7. **Inner plexiform layer** contains **axodendritic synapses** between the axons of bipolar cells and the dendrites of ganglion cells. The processes of amacrine cells are also located in this layer.
8. The **ganglion cell layer** contains the **somata of ganglion cells**, which form the final link in the retina's neural chain. Of the two types of ganglion cells, the majority (approximately 97% of ganglion cells) are those that function in vision. A very small minority function in the diurnal rhythm by projecting, ***indirectly***, to the pineal body informing that gland whether it is daylight or night. Only the ganglion cells that function in the sensation of vision are described here.
   a. **Structure—ganglion cells** are typical neurons that project their axons to a specific region of the retina called the **optic disc**. There are three types of cells: **midget**, **diffuse**, and **stratified ganglion cells**.
   b. **Function—ganglion cells** are activated by **hyperpolarization of rods** and **cones** and generate an **action potential**, which is transmitted to horizontal and amacrine cells and carried to the visual relay system in the brain.
9. The **optic nerve fiber layer** consists primarily of the **unmyelinated axons** of ganglion cells, which form the fibers of the **optic nerve**. As each fiber pierces the sclera, it acquires a myelin sheath.
10. The **inner limiting membrane** consists of the terminations of Müller cell processes and their basement membranes.

CLINICAL CONSIDERATIONS

Leber congenital amaurosis (LCA) is a rare inherited condition that results in blindness in newborn children. Numerous genes are responsible for this condition, which is characterized by lack of pupillary response, anomalous embryology of rods and cones, and lack of vision. Until a few years ago, no treatment was available for this disease, but individuals whose biallelic mutation of the *RPE65* gene was responsible for LCA have been helped by the administration of gene therapy. In October 2017, one of the Advisory Committees of the Food and Drug Administration (FDA) recommended that the FDA endorse gene therapy treatment for patients with biallelic mutations of the *RPE65* gene.

F. Accessory structures of the eye

1. **The conjunctiva** (**transparent mucous membrane**), a **stratified columnar epithelium** possessing many **goblet cells**, lines the eyelids and is reflected onto the anterior portion of the eyeball to the cornea, where it becomes continuous with the corneal epithelium. It is separated by a basal lamina from an underlying lamina propria of loose connective tissue.

CLINICAL CONSIDERATIONS

Conjunctivitis, an inflammation of the conjunctiva producing red sclera and a discharge, may be caused by bacteria, viruses, parasites, and allergens. Some forms of conjunctivitis are contagious and may cause blindness if left untreated.

2. The **eyelids**, lined internally by conjunctiva and externally by skin that is elastic and covers a supportive framework of **tarsal plates**, contain highly modified **sebaceous glands** (meibomian glands), smaller **modified sebaceous glands** (glands of Zeis), and **sweat glands** (glands of Moll).
3. **Lacrimal apparatus** (Fig. 19.6)
   a. The **lacrimal gland**, a compound **tubuloacinar gland** with secretory units that are surrounded by an incomplete layer of **myoepithelial cells**, produces **lacrimal fluid** (**tears**) composed mostly of water containing **lysozyme**, an antibacterial enzyme. Tears drain from the lacrimal gland via 6 to 12 ducts into the conjunctival **fornix**, from which the tears flow over the cornea and conjunctiva, keeping them moist. Tears then enter the lacrimal puncta, leading to lacrimal ducts (canaliculi).
   b. **Lacrimal ducts** (**lacrimal canaliculi**) are lined by a **stratified squamous epithelium** and unite to form a common canaliculus, which empties into the lacrimal sac.
   c. The **lacrimal sac** is lined by a **pseudostratified ciliated columnar epithelium**.
   d. The **nasolacrimal duct** is the inferior continuation of the lacrimal sac and is also lined by a **pseudostratified ciliated columnar epithelium**. The duct empties into the floor of the nasal cavity.

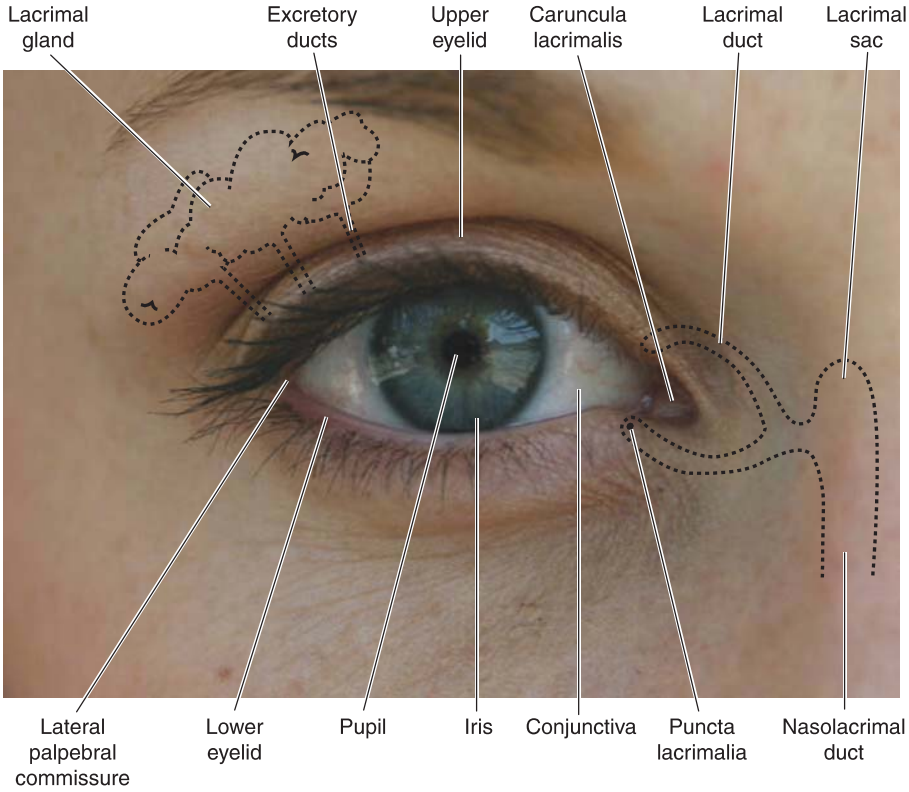


FIGURE 19.6. External anatomy of the eye. (Reprinted with permission from Hiatt JL, Gartner LP. *Textbook of Head and Neck Anatomy*. 4th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2010:164.)

IV. SENSE OF HEARING AND BALANCE—EAR (VESTIBULOCOCHLEAR APPARATUS)

The ear consists of three parts: the **outer** (**external**) **ear**, which receives sound waves; the **middle ear**, through which sound waves are transmitted; and the **internal ear**, where sound waves are transduced into nerve impulses. The vestibular organ, responsible for equilibrium, is also located in the inner ear.

A. The outer (external) ear (Fig. 19.7) has two regions, the auricle (pinna) and the external acoustic meatus (ear canal).

1. The **auricle (pinna)** is composed of irregular plates of **elastic cartilage** covered by **thin skin**.
2. The **external auditory meatus** (**ear canal**) is lined by **skin** containing hair follicles, sebaceous glands, and **ceruminous glands**, which are modified sweat glands that produce **earwax** (**cerumen**). The **external auditory meatus** ends at the tympanic membrane, which is covered by **skin** on its external surface and by a **simple cuboidal epithelium** on its inner surface. It possesses **fibroelastic connective tissue** interposed between its two epithelial coverings. The tympanic membrane **transmits sound vibrations** that enter the ear to the ossicles in the middle ear.

B. Middle ear (tympanic cavity) (see Fig. 19.7)

1. The tympanic cavity, filled with air, contains the three bony **ossicles** (**malleus**, **incus**, and **stapes**), which **transmit vibrations of the tympanic membrane (eardrum) to the oval window** (a membrane-covered opening in the bony wall of the **cochlea**).
   a. The bony ossicles, **malleus**, **incus**, and **stapes**, are attached to each other in a chain-like formation between the tympanic membrane and the oval window, a membrane-covered opening in the bony labyrinth. The malleus is attached to the tympanic membrane, whereas the stapes is attached to the membrane of the oval window. The middle ossicle, the incus, is interposed between the malleus and the stapes. Small ligaments interconnect the ossicles.

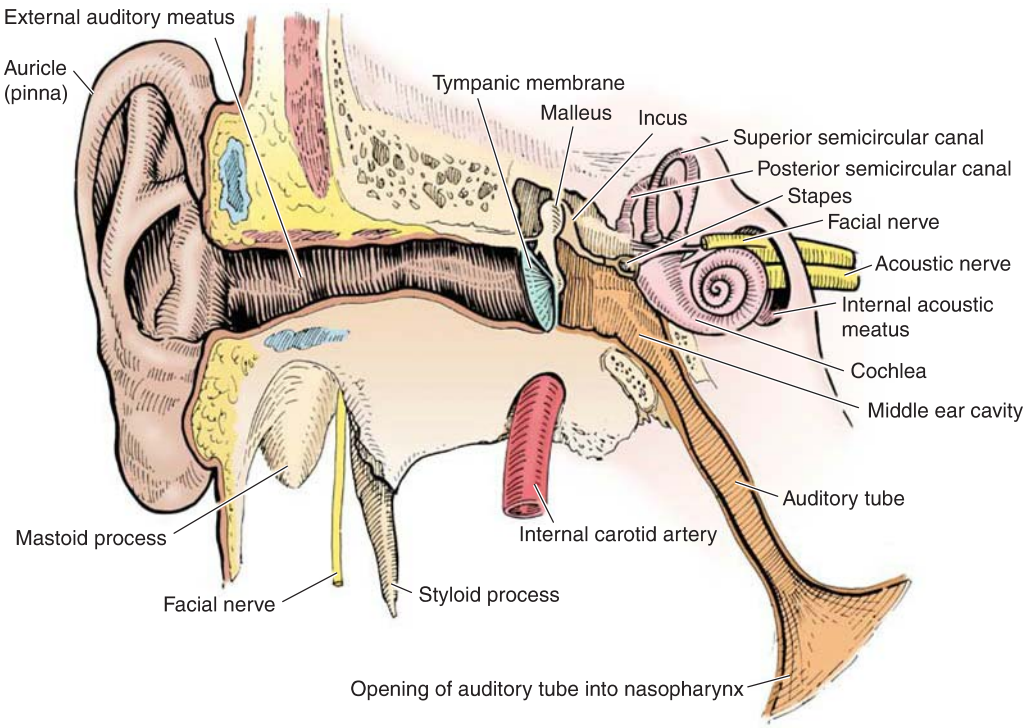


FIGURE 19.7. The external, middle, and inner ears. (Reprinted with permission from Hiatt JL, Gartner LP. *Textbook of Head and Neck Anatomy*. 2nd ed. Baltimore, MD: Williams & Wilkins; 1987:309.)

b. Two separate muscles, innervated by branches of individual CNs, serve to control the functioning of these ossicles. The **tensor tympani muscle** maintains tension on the tympanic membrane and is innervated by a branch of the trigeminal nerve (CN V). The **stapedius muscle** dampens the movement of the stapes on the membrane covering the oval window. It is innervated by a branch of the facial nerve (CN VII).

c. The bony ossicles, as a group, function in modulating movements of the tympanic membrane and in amplifying the sound waves by applying pressure on the membrane covering the oval window in the cochlea.

2. The middle ear, connected to the mastoid air cells posteriorly and to the nasopharynx anteriorly, is lined by a **simple squamous epithelium**, which changes to **pseudostratified ciliated columnar epithelium** near its opening to the auditory tube and along the external aspect of the tympanic membrane. The middle ear has a **lamina propria** composed of dense connective tissue tightly adherent to the bony wall.

CLINICAL CONSIDERATIONS

Conductive hearing loss results from a defect in the conduction of sound waves in the external or middle ear. This condition may be caused by **otitis media**, a common inflammation of the middle ear; **obstruction** by a foreign body; impacted **earwax**; **perforated** tympanic membrane; or **otosclerosis** of the middle ear.

C. The temporal bone contains a space, known as the *bony labyrinth*, that houses the *inner ear*.

1. The **bony labyrinth**, composed of the semicircular canals, vestibule, and cochlea, is filled with **perilymph** and houses the **membranous labyrinth**, which is filled with **endolymph** (Fig. 19.8).

a. Semicircular canals house the **semicircular ducts** of the membranous labyrinth.

b. The **vestibule** houses two small sacs, **saccule** and **utricle**, specialized regions of the membranous labyrinth.

c. The **cochlea**, which winds two and a half times around the blood vessel and spiral ganglion–containing bony core (the **modiolus**), is subdivided into three spaces: the **scala vestibuli** and **scala tympani**, *which both belong to the bony labyrinth* and are filled with **perilymph**, and the **scala media** (**cochlear duct**), which *belongs to the membranous labyrinth* and is filled with **endolymph**. The **scala tympani** has a membrane covering it as it opens at the **round window** into the middle ear cavity and, as indicated earlier, the **scala vestibuli** has a similar membrane-covered opening at the **oval window** into the middle ear cavity.

2. The **membranous labyrinth** is filled with **endolymph** and possesses various **sensory structures** that are **specializations of the epithelium** that encloses the membranous labyrinth (see Fig. 19.8).

a. The **saccule and utricle** (within the **vestibule**) are sac-like bodies composed of a thin sheath of connective tissue lined by **simple squamous epithelium**. Each gives rise to a duct; the two ducts join, forming the **endolymphatic sac**. They possess small, specialized regions called **maculae**, which contain **neuroepithelial hair cells**, supporting cells, and a gelatinous layer (**otolithic membrane**).

(1) Vestibular hair cells are **neuroepithelial cells** that contain many mitochondria and a well-developed Golgi complex. They possess 50 to 100 elongated, **rigid stereocilia** (sensory microvilli) arranged in rows and a single cilium (**kinocilium**). These cilia extend from the apical surface of the hair cells into the otolithic membrane. They function in the **detection of linear acceleration**.

(a) The two types of vestibular hair cells are: **type I hair cells** (**bulbar**), which are almost completely surrounded by a **cup-shaped afferent nerve ending**, and **type II hair cells** (columnar), which make contact with **small afferent terminals** containing synaptic vesicles.

(2) Supporting cells are generally columnar and possess a round basal nucleus, many microtubules, and an extensive terminal web.

(3) The **otolithic membrane** is a **gelatinous layer** of glycoprotein that contains small calcified particles called **otoliths** or **otoconia**.

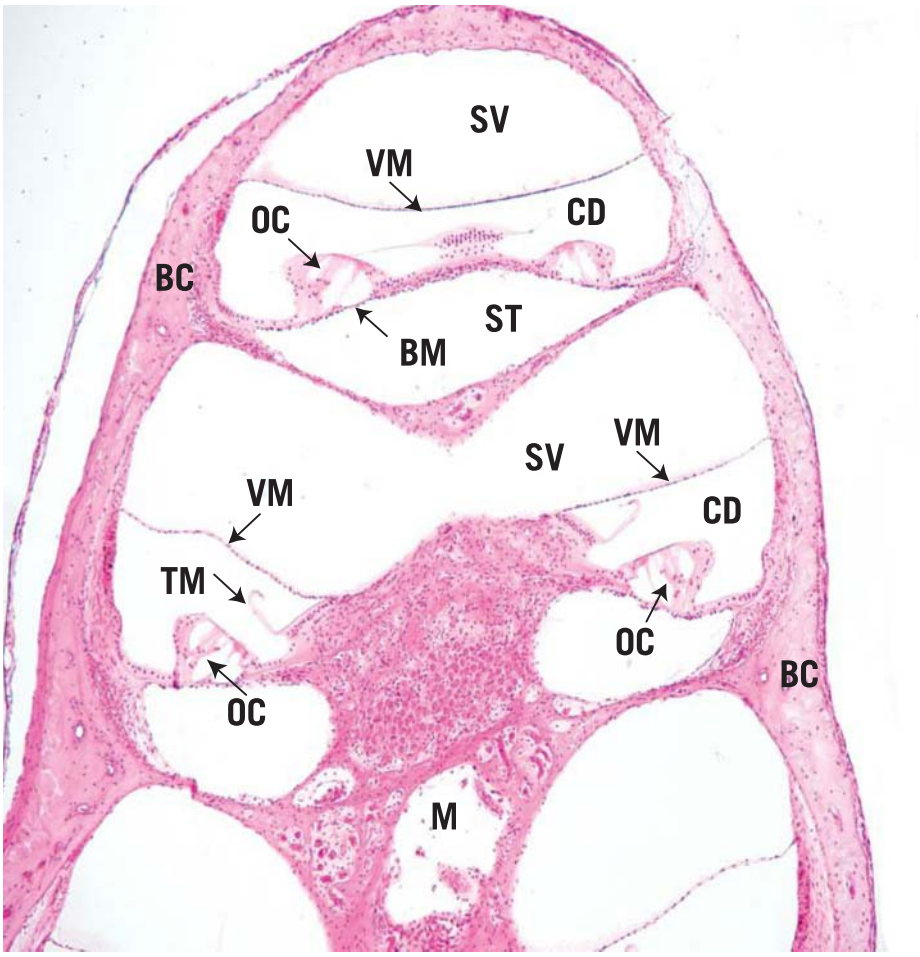


FIGURE 19.8. This is a low-power light micrograph (×56) through the apical region of the cochlea. Note the bony cochlea (BC), the modiolus (M), the vestibular membrane (VM) separating the scala vestibuli (SV) from the cochlear duct (CD). Observe the basilar membrane (BM) with the organ of Corti (OC), the tectorial membrane (TM), as well as the scala tympani (ST).

b. Semicircular ducts are continuous with and arise from the **utricle**. The three semicircular ducts are perpendicular to each other so that they can **detect angular acceleration** of the head in three-dimensional space (see Fig. 19.7).
  (1) The **ampullae** are dilated regions of the semicircular ducts near their junctions with the utricle.
  (2) Cristae ampullares, specialized **sensory regions** within the ampullae of the semicircular ducts, are similar to maculae but have a thicker, conical glycoprotein layer (**cupula**), which does not contain otoliths.

c. The **endolymphatic duct** ends in the expanded endolymphatic sac.

d. Endolymphatic sac has an epithelial lining containing **electron-dense** columnar cells, which have an irregularly shaped nucleus, and **electron-lucent** columnar cells, which possess long microvilli, many pinocytic vesicles, and vacuoles. It may function in resorption of endolymph and contains **phagocytic cells** (macrophages, neutrophils) in its lumen.

e. Scala media (**cochlear duct**) is a specialized diverticulum of the saccule that contains the **spiral organ of Corti** (Figs. 19.9 and 19.10; also see Fig. 19.8). It is bordered above by the **scala vestibuli** and below by the **scala tympani** of the bony cochlea. These perilymph-containing scalae communicate with each other at the **helicotrema** at the apex of the cochlea. The principal components of the scala media are:
  (1) The **vestibular (Reissner) membrane**, composed of two layers of flattened squamous epithelium separated by an intervening basement membrane, helps maintain the high

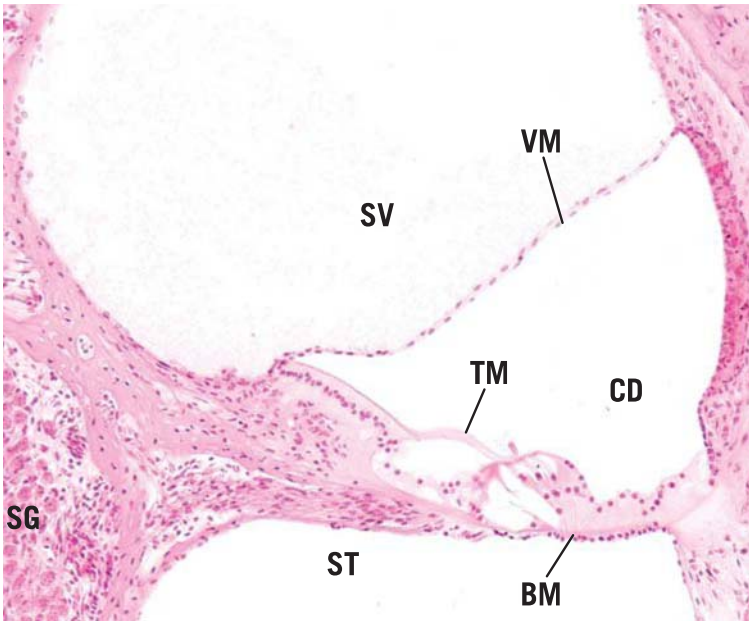


FIGURE 19.9. Light micrograph of the cochlea (×132). Note the spiral ganglion (SG), scala tympani (ST), basilar membrane (BM), scala vestibuli (SV), vestibular membrane (VM), tectorial membrane (TM), and the cochlear duct (CD).

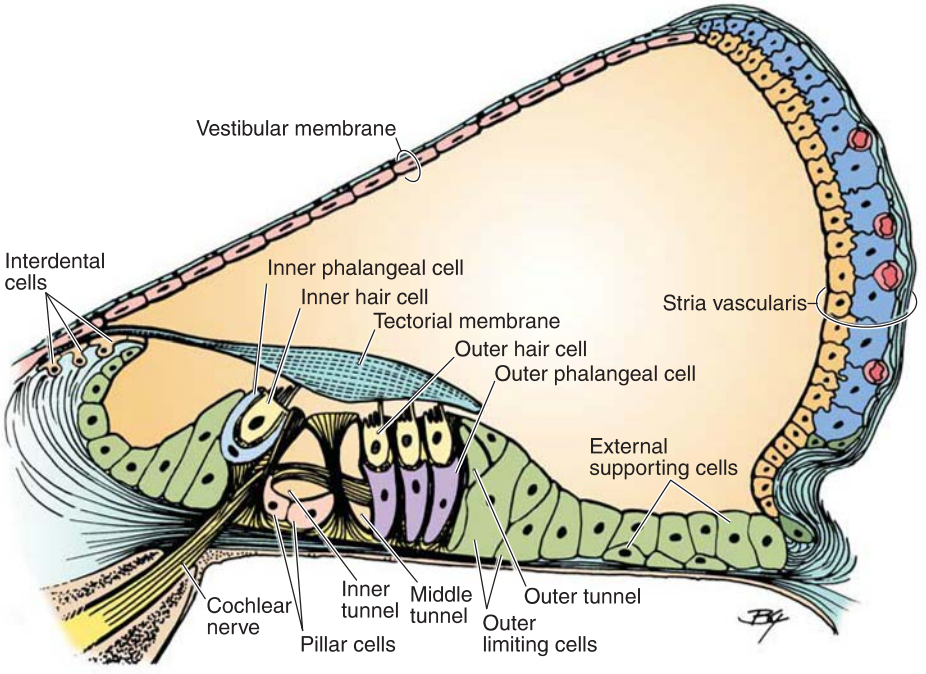


FIGURE 19.10. The cochlear duct and the spiral organ of Corti. (Adapted with permission from Dellmann HD. *Textbook of Veterinary Histology.* 4th ed. Baltimore, MD: Williams & Wilkins; 1993:332.)

ionic gradients between the perilymph in the scala vestibuli and the endolymph in the cochlear duct.

(2) **Stria vascularis**, composed of basal, intermediate, and marginal cells, is a **vascularized** pseudostratified epithelium that lines the lateral aspect of the cochlear duct and may **secrete endolymph**.

(3) The **spiral prominence** is an epithelium-covered protuberance that extends the length of the cochlear duct. This epithelium is continuous with that of the stria vascularis and is reflected onto the basilar membrane, where it follows an indentation to form the **external spiral sulcus**. The cells of this epithelium become cuboidal and continue onto the basilar membrane, where they are known as the **cells of Claudius**, which overlie the polyhedral **cells of Boettcher**.

(4) The **basilar membrane**, a thick layer of amorphous material containing **keratin-like fibers**, has two zones, the medial **zona arcuata** and the lateral **zona pectinata**. The ***width*** of the basilar membrane extends from near the spiral lamina (at the modiolus) to the tympanic lip of the limbus spiralis. The ***length*** of the basilar membrane extends from its ***base***, at the oval window, to its ***apex***, near the helicotrema. Because its ***base*** is firm and slim this region reacts to **high-pitched** (**high-frequency**) **sound**, whereas its ***apex*** is supple and broad, thus it reacts more to **low-pitched** (**low-frequency**) **sound**. The gradual increase in stiffness from its apex to its base is responsible for the gradation in the pitch perceived by the organ of Corti.

(5) The **tectorial membrane**, secreted by the interdental cells of the spiral sulcus, **makes contact with the processes of the hair cells**.

(6) The **spiral organ of Corti**, composed of **hair cells** and various **supporting cells**, lies upon both parts of the basilar membrane and displays both the **inner tunnel of Corti** and the **outer tunnel** (**space of Nuel**), which communicate with each other via extracellular spaces. In the human this organ is about 32 mm in length.

(7) **Hair cells** of the organ of Corti are **neuroepithelial cells** containing a round basal nucleus surrounded by many mitochondria. They possess many long, **stiff stereocilia** (arranged in a W formation) on their free surfaces, as well as a **basal body** (but no kinocilium). Hair cells **function** in the **reception of sound** and possibly pain reception and can respond to different sound frequencies. The two types of hair cells are:

   (a) **Inner hair cells** (**IHCs**) are about 3,500 in number and are organized in a **single row** along the entire length of the cochlear duct and receive numerous afferent synaptic terminals on their basal surface. At least 90% of sensory fibers of the auditory nerve contact the IHCs and deliver their information to the auditory nucleus.

   (b) **Outer hair cells** (**OHCs**), about 12,000 in number, are organized in **three or more rows** and are ensconced within a cup-shaped afferent nerve ending, where synaptic contacts are made. They appear to function as **cochlear amplifiers** where they amplify low sound volumes entering the cochlea. They are able to do so because when the cell membrane of the OHC becomes depolarized, chloride ions uncouple from the membrane protein **prestin**, causing the protein to alter its three-dimensional conformation. The altered shape of prestin causes contraction of the OHC, which, in turn, elevates the basilar membrane, thereby increasing the extent of its vibration, resulting in amplification of the signal. OHCs may also act as pain receptors.

(8) **Inner and outer pillar cells** of the organ of Corti are intimately associated with each other; both types rest on the basilar membrane. They enclose and support the inner tunnel of Corti, which lies between the inner and outer pillar cells. Inner and outer pillar cells possess a wide base and have elongated processes, which contain microtubules, intermediate filaments, and actin filaments.

(9) **Inner and outer phalangeal cells** of the organ of Corti are intimately associated with IHC and OHC, respectively. They also support the slender nerve fibers that form synapses with the hair cells.

(10) **Cells of Hensen** and **border cells** of the organ of Corti delineate the inner and outer borders of the spiral organ of Corti.

CLINICAL CONSIDERATIONS

Nerve deafness (**sensorineural hearing loss**), the most common type of hearing loss, results from the damage or loss of hair cells or from a **lesion** in any of the nerves transmitting impulses from the spiral organ of Corti to the brain. It may be caused by diseases, such as infection; reduced oxygen tension; exposure to drugs, which include certain anticancer medications, various antibiotics, and even some diuretics; and sudden exposure to an extremely loud noise (as an explosion) or prolonged exposure to loud noises. The most sensitive spectrum of hair cells are those located at the base (near the oval window) of the basilar membrane.

Age-related hearing loss was once considered to be related to hair cell loss in the organ of Corti; however, recent investigations demonstrated that the culprit was damage to the auditory nerve fiber terminals. Therefore, even though the hair cells were performing their function by releasing their neurotransmitter substances, the terminals of the auditory nerve fibers were damaged to such an extent that they were unable to respond to the signal. As the individuals aged, more and more of their synapses were destroyed, and, even though the patients heard that something was said, they were unable to recognize the words, especially in noisy conditions.

3. **Auditory function of the inner ear**
   - **a.** Movement of the stapes at the oval window causes disturbances in the perilymph, which cause deflection of the **basilar membrane**. Oscillations set in motion at the oval window are dissipated at the secondary tympanic membrane covering the **round window** of the cochlea. (At a very loud concert, the amount of energy absorbed is very high, and it may take up to 72 hours for it to be dissipated. A residual humming noise may be heard for 2–3 days.)
   - **b.** Large areas of the basilar membrane vibrate at many frequencies. However, optimal vibrations are detected at only specific areas. Sound waves of low frequency are detected farther away from the oval window.
   - **c.** The **pillar cells** attached to the basilar membrane move laterally in response to this deflection, in turn causing a lateral shearing of the stereocilia of the sensory hair cells of the organ of Corti against the tectorial membrane.
   - **d.** **Movement of the stereocilia** is transduced into electrical impulses that travel via the **cochlear nerve** to the brain.
4. **Vestibular function of the inner ear**
   - **a.** A change in the position of the head causes a flow of the endolymph in the semicircular ducts (**circular movement**) or in the saccules and utricles (**linear movement**).
   - **b.** Movement of the endolymph in the semicircular ducts displaces the cupula overlying the **cristae ampullares**, causing bending of the stereocilia of the sensory hair cells.
   - **c.** Movement of the endolymph in the saccules and utricles displaces the **otoliths**. This deformation is transmitted to the **maculae** via the overlying gelatinous layer, causing bending of the stereocilia of the sensory hair cells.
   - **d.** In both cases, **movement of the stereocilia** is transduced into **electrical impulses**, which are transmitted to the brain via **vestibular nerve fibers**.

CLINICAL CONSIDERATIONS

Ménière disease is an inner ear disorder causing hearing loss, vertigo, nausea, tinnitus, and vomiting. It is related to excess fluid in the endolymphatic duct resulting in increased pressure of endolymph causing dilations along the entire membranous labyrinth. Whether the excess fluid is due to increased production or to interference with its drainage (or, possibly, a combination of the two) is not known, but the increased pressure interferes with both balance and hearing. Although it usually affects only one side, eventually the other side will also be affected in almost 50% of individuals who have this condition. The condition has a cyclic component, in that it appears to resolve itself, only to return with increasing severity. Eventually the cycling stops, but the inner ear becomes so damaged that the patient has relentless problems with balance, a constant tinnitus, and complete, or nearly complete loss of hearing. Although no cure is available for Ménière disease, drugs are available to treat the vertigo and nausea. Lifestyle changes are also recommended, such as lowering sodium intake, eliminating alcohol and coffee from the diet, and stopping tobacco use; but, in severe cases, surgery may be required for vestibular neurectomy.

Review Test

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A neurologist is testing the corneal reflex of a patient by touching the cornea with a wisp of cotton. Which CN is she testing?

(A) CN I
(B) CN II
(C) CN III
(D) CN IV
(E) CN V

2. A patient exhibiting a high intraocular pressure in both eyes is symptomatic for

(A) cataract.
(B) detached retina.
(C) glaucoma.
(D) conjunctivitis.
(E) presbyopia.

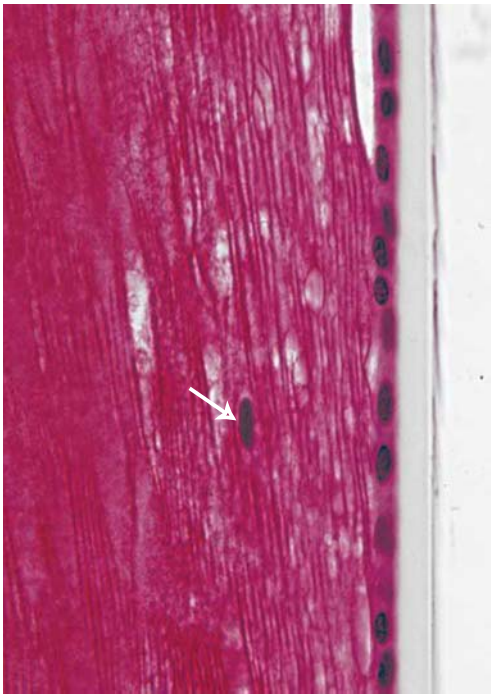
3. An ophthalmologist is fitting his patient, a female in her early twenties, with contact lenses. He reminds her to be careful not to commit the hazardous conduct that more than 85% of contact wearers commit. Which is the most common hazardous behavior?

(A) Swimming with the contacts in their eyes
(B) Sleeping all night long with the contact lenses in their eyes
(C) Taking a nap with the contact lenses in their eyes
(D) Storing the contact lenses in tap water
(E) Wearing contact lenses when their eyes are infected

4. An older homeless patient is complaining to the ophthalmologist that he is having difficulties recognizing people's faces but has no problems with seeing things at the periphery. What should the ophthalmologist suspect to be the diagnosis?

(A) Macular degeneration
(B) Detached retina
(C) Glaucoma
(D) Conjunctivitis
(E) Presbyopia

Question 5 is based on the following photomicrograph.



5. An elderly patient with alterations in the cells as indicated by the arrow likely has which condition?

(A) Cataract
(B) Detached retina
(C) Glaucoma
(D) Conjunctivitis
(E) Presbyopia

6. A patient with overabundance of fluid in her endolymphatic duct is suffering from which condition?

(A) Glaucoma
(B) Ménière disease
(C) Otitis media
(D) Conductive hearing loss
(E) Nerve deafness

7. Which specialized receptor exhibits a large ovoid capsule consisting of many concentric lamellae each separated by a space containing tissue fluid?

(A) Cold receptors
(B) Pacinian corpuscles
(C) Ruffini endings
(D) Meissner corpuscles
(E) Krause end bulb

8. The ENT is examining a patient and determines that the patient is suffering from conductive hearing loss. He notices that the possible cause of the patient's hearing loss is due to

(A) excess endolymph production.
(B) excess perilymph production.
(C) damaged IHCs.
(D) impacted earwax.
(E) lack of cerumen in the ear canal.

9. Damage to which cell or structure is the principal cause of age-related hearing loss?

(A) IHCs
(B) OHCs
(C) Tectorial membrane
(D) Inner pillar cells
(E) Auditory nerve fiber terminals

10. Which cells in the inner ear are involved in detecting movements of the head?

(A) Hair cells in the maculae
(B) Outer pillar cells
(C) Inner pillar cells
(D) Cells of Hensen
(E) Hair cells in the organ of Corti

Answers and Explanations

1. **E.** The neurologist is testing for the CN that provides sensory innervation to the cornea and that nerve is the ophthalmic division of the trigeminal nerve (CN V).
2. **C.** High intraocular pressure is a symptom of glaucoma. This condition prohibits the aqueous humor from escaping from the anterior chamber of the eye via the canal of Schlemm. If it is left untreated, a gradual loss of peripheral sight occurs; over time, blindness results.
3. **C.** Almost 41 million Americans wear contacts, and 93% of them wear soft lenses; 99% of the surveyed group have admitted to committing at least one hazardous behavior. The most common of these behaviors were taking a nap while wearing the lenses (87%), showering with the lenses in the eyes, swimming while wearing the lenses (61%), adding fresh cleaning solution to the old solution (55%), not replacing the lenses at suggested intervals (50%), sleeping all night long while wearing the lenses (50%), using tap water instead of cleaning solution to rinse the contact lenses (35%), continuing to wear contacts during eye infection (30%), and storing the lenses in tap water rather than in cleaning solution (17%). The use of tap water is the riskiest of these behaviors because transferring microbes from the water into the eye causes eye infections.
4. **A.** Age-related macular degeneration (AMD) is a disease of the retina located in the central region of the macula, hence affecting central vision. As its name implies, it is a disease of aging, occurring usually after the age of 50 years. The two forms are dry and wet AMD.
5. **A.** A cataract is an opacity of the lens resulting from the accumulation of pigment or other substances in the lens fibers, which scatter the light entering the lens, thus preventing sharp focusing of the light on the retina. It is often associated with **aging**, and, if untreated, it may lead to a gradual loss of vision. When the opacity becomes severe, an ophthalmologist may remove and replace the affected lens with a man-made lens, restoring clear vision.
6. **B.** An overabundance of endolymph in the endolymphatic duct causes vertigo, nausea, hearing loss, tinnitus, and vomiting, all symptoms of Ménière disease.
7. **B.** Pacinian corpuscles are usually macroscopic. Their capsules are composed of several lamellae containing fibroblasts and collagen fibers. The lamellae are separated by sparse amounts of tissue fluid. Pacinian corpuscles respond to vibrations and pressure that distort the lamellae.
8. **D.** Conductive hearing loss results from a defect in the conduction of sound waves in the external or middle ear. This condition may be caused by otitis media, a common inflammation of the middle ear; obstruction by a foreign body; perforated tympanic membrane; or otosclerosis of the middle ear; or, in this patient's case, impacted earwax.
9. **E.** Age-related hearing loss was considered to be related to hair cell loss in the organ of Corti; however, recent investigations have demonstrated that the culprit was damage to the auditory nerve fiber terminals. Therefore, even though the hair cells were performing their function by releasing their neurotransmitter substances, the terminals of the auditory nerve fibers were damaged to such an extent that they were unable to respond to the signal.
10. **A.** Neuroepithelial hair cells in the maculae of the saccule and the utricle detect linear movement of the head. These cells are connected to the vestibular portion of the acoustic nerve.

Comprehensive Examination

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. Which of the following statements concerning ribonucleic acid (RNA) synthesis is true?

(A) RNA synthesis does not require deoxyribonucleic acid (DNA) to act as a template.
(B) Syntheses of ribosomal RNA, messenger RNA, and transfer RNA are all catalyzed by the same RNA polymerase.
(C) To yield messenger RNA, introns are excised, whereas exons are spliced together.
(D) Protein moieties are removed from messenger ribonucleoproteins (mRNPs) within the nucleolus, resulting in functional messenger RNAs to exit via the nuclear pores.
(E) The start codon for RNA synthesis is UAG.

2. An older female patient was diagnosed with osteoporosis. Which of the following factors is primarily responsible for causing that condition?

(A) Decreased bone formation
(B) Lack of physical exercise
(C) Diminished estrogen secretion
(D) Calcium deficiency
(E) Increased bone formation

3. Which of the following bases is unique to RNA?

(A) Thymine
(B) Adenine
(C) Cytosine
(D) Guanine
(E) Uracil

4. A patient with pancreatitis has malfunctioning centroacinar cells. Which of the following is affected by this problem?

(A) Enzyme-poor alkaline fluid
(B) Pancreatic digestive enzymes
(C) Secretin
(D) Cholecystokinin
(E) Glucagon

5. Individuals whose zona fasciculata cells of the adrenal cortex do not function properly will have lowered levels of

(A) mineralocorticoids.
(B) glucagon.
(C) epinephrine.
(D) aldosterone.
(E) glucocorticoids.

6. Which of the following statements is correct about the bony joints of patients?

(A) Long bones are generally united by synarthroses.
(B) Diarthroses are classified as synovial joints.
(C) Type A cells of the synovial membrane secrete synovial fluid.
(D) Type B cells of the synovial membrane are phagocytic.
(E) Synarthroses are usually surrounded by a two-layered capsule.

7. A hematologist can use all of the following characteristics to distinguish neutrophils from basophils histologically except one. Which one is the exception?

(A) Size of specific granules
(B) Shape of the nucleus
(C) Number of azurophilic granules
(D) Presence or absence of peroxidase
(E) Presence of mitochondria

8. A patient who is a long-time user of chewing tobacco went to see his family practitioner because he noticed several whitish, thick, painless patches on the lining of his cheeks. The physician should consider the diagnosis to be

(A) aphthous ulcers.
(B) adenocarcinoma.
(C) keloids.
(D) oral leukoplakia.
(E) epidermolysis bullosa.

9. Primordial follicles of the ovary possess

(A) a layer of cuboidal follicular cells.
(B) an oocyte arrested in prophase of meiosis I.
(C) an oocyte arrested in metaphase of meiosis II.
(D) well-defined theca interna and theca externa.
(E) a thick zona pellucida.

10. A medical student who is doing her rotation in ENT is asked by her resident which of the following structures belong to the organ of Corti.

(A) Saccule
(B) Utricle
(C) Cristae ampullares
(D) Otolithic membrane
(E) Vestibular membrane

11. A first-year medical student, looking at an electron micrograph of the nucleus, is asked to point out the euchromatin and identify which of the following is the correct statement about that structure.

(A) It constitutes about 90% of the chromatin.
(B) It appears as basophilic clumps of nucleoprotein when seen under the light microscope.
(C) It is concentrated near the periphery of the nucleus.
(D) It is transcriptionally active.
(E) It is transcriptionally inactive.

12. Intercalated disks function in which one of the following?

(A) End-to-end attachments of smooth muscle cells
(B) Intercellular movement of large proteins
(C) Ionic coupling of cardiac muscle cells
(D) Storage of Ca^{2+}
(E) Release of neurotransmitters

13. A 28-year-old female complains to her family physician about unwanted weight loss, feeling of agitation, and constantly being warm. The physician suspects overstimulation of her thyroid gland and orders a blood test to check her thyroid-stimulating hormone (TSH) levels. What histologic changes does TSH stimulation involve?

(A) Binding of TSH to receptors on the apical plasma membrane
(B) Formation of apical microvilli
(C) Exocytosis of colloid droplets
(D) Change in cell shape from flattened to columnar
(E) Secretion of lysosomes from the basal cell surface

14. Which one of the following statements about the development of the tooth crown is true?

(A) The enamel organ is derived from ectomesenchyme (neural crest).
(B) The dental papilla is derived from the epithelium.
(C) The four-layer enamel organ appears during the cap stage.
(D) Dentin and enamel are formed during the appositional stage.
(E) Cementum is formed at the same time as enamel.

15. Which one of the following statements concerning liver sinusoids is true?

(A) Their lining includes Ito cells (fat-storing cells).
(B) They receive bile from the hepatocytes.
(C) They are lined by nonfenestrated endothelial cells.
(D) The space of Disse is located between sinusoidal cells and hepatocytes.
(E) Sinusoids convey blood from the central vein to the portal vein.

16. A young college student had nausea, vomiting, visual disorders, and muscular paralysis after eating canned tuna fish. The probable diagnosis is botulism, caused by ingestion of the *Clostridium botulinum* toxin. The physiologic effect of this toxin is to

(A) inactivate acetylcholinesterase.
(B) bind to and thus inactivate acetylcholine receptors at myoneural junctions.
(C) prevent release of calcium ions from the sarcoplasmic reticulum, thus inhibiting muscle contraction.
(D) inhibit release of acetylcholine from presynaptic membranes.
(E) inhibit hydrolysis of adenosine triphosphate during the contraction cycle.

17. Which of the following statements about nucleosomes is true?

(A) Histones form the nucleosome core around which the double helix DNA is wound.
(B) Nucleosomes without histones form the structural unit of the chromosome.
(C) Nucleosomes are composed of RNA molecules and two copies each of four different histones.
(D) Histone H1 forms the core of the nucleosome.
(E) Nucleosomes are linked together with RNA.

18. A high school student complains of fatigue and a sore throat. She has swollen, tender lymph nodes and a fever. Blood test results show an increased white blood cell count with many atypical lymphocytes; the number and appearance of the erythrocytes are normal. This student is likely to have

(A) acquired immune deficiency syndrome (AIDS).
(B) pernicious anemia.
(C) infectious mononucleosis.
(D) Hodgkin disease.
(E) factor VIII deficiency.

19. Which one of the following statements about the gallbladder is true?

(A) The gallbladder dilutes bile.
(B) Bile enters the gallbladder via the common bile duct.
(C) Bile leaves the gallbladder via the cystic duct.
(D) The gallbladder is lined by a simple squamous epithelium.
(E) Secretin stimulates the wall of the gallbladder to contract, forcing bile from its lumen.

20. Newborn infants have a larger accumulation of brown fat than do adults; in what way is the mitochondria in brown fat cells different from most other mitochondria?

(A) Instead of the orthodox configuration, they assume the condensed form in response to the uncoupling of oxidation from phosphorylation.
(B) They are unable to divide.
(C) They possess the enzymes of the Krebs cycle in their cristae.
(D) They contain elementary particles in their matrix.
(E) They do not contain DNA.

21. Which one of the following components is present in muscular arteries but absent from elastic arteries?

(A) Fenestrated membranes
(B) Vasa vasorum
(C) Factor VIII
(D) Thick, complete internal elastic lamina
(E) Smooth muscle cells

22. Which of the following statements is true concerning the pancreas of a healthy patient?

(A) Islets of Langerhans secrete enzymes.
(B) It possesses mucous acinar cells.
(C) The endocrine pancreas has more β cells than δ cells.
(D) Its α cells secrete insulin.
(E) Its δ cells secrete amylase.

23. A patient with gastroesophageal reflux disease may have a tumor of diffuse neuroendocrine system (DNES) cells that produce which of the following substances?

(A) Somatostatin
(B) Gastrin
(C) Secretin
(D) Cholecystokinin
(E) Urogastrone

24. A pediatrician sees a child with short stature and suspects that the child has a deficiency or an excess of which of the following vitamins?

(A) Vitamin A
(B) Vitamin C
(C) Vitamin D
(D) Vitamin K
(E) Vitamin B

25. The intercellular spaces in the stratum spinosum of the epidermis contain lipid-containing sheets that are impermeable to water. This material is released from

(A) keratohyalin granules.
(B) Langerhans cells.
(C) membrane-coating granules.
(D) sebaceous glands.
(E) melanosomes.

26. A hematologist can recognize a basophilic erythroblast by knowing several of its characteristics, one of which is that its

(A) nucleus has a fine chromatin network.
(B) nucleus is in the process of being extruded.
(C) cytoplasm contains specific granules.
(D) cytoplasm is pink and reveals a dense reticulum.
(E) nucleus is bilobed.

27. A pathologist recognizes the ileum because of its several characteristics, including the presence of

(A) rugae.
(B) Peyer patches.
(C) Brunner glands.
(D) Parietal cells.
(E) chief cells.

28. A 25-year-old woman complains about a frequently recurring painful lesion on her upper lip that exudes a clear fluid. She probably has

(A) oral leukoplakia.
(B) herpetic stomatitis.
(C) aphthous ulcer.
(D) bullous pemphigoid.
(E) malignant melanoma.

29. Which of the following statements concerning the functions of the skin is true?

(A) Infrared radiation, necessary for synthesis of vitamin D, is absorbed by the skin.
(B) The skin provides no protection against desiccation.
(C) The skin contains temperature receptors and plays a role in regulating body temperature.
(D) Melanin is synthesized by melanocytes, which are located in the dermis.
(E) Sunscreen with a sun protection factor rating of 15 or higher protects the skin from harmful effects caused by ultraviolet light.

30. A 55-year-old female patient sees her urologist who, based on one of the following signs or symptoms, supposes that she has glomerulonephritis. Which is that sign or symptom?

(A) Hypotonic urine
(B) Polyuria
(C) Proteinuria
(D) Dehydration
(E) Polydipsia

31. A microscopic image displays that the structure biopsied is lined by a stratified squamous keratinized epithelium. Which of the following was biopsied?

(A) Rectum
(B) Esophagus
(C) Pylorus
(D) Jejunum
(E) Anus

32. A premature infant has labored breathing, which is eventually alleviated by administration of glucocorticoids. The most probable diagnosis is

(A) immotile cilia syndrome.
(B) emphysema.
(C) hyaline membrane disease.
(D) asthma.
(E) chronic bronchitis.

33. Which of the following statements concerning the cribriform plate is true?

(A) It is the inner layer of the alveolar bone.
(B) It lacks Sharpey fibers.
(C) It is also known as the spongiosa.
(D) It is composed of cancellous bone.
(E) Normally, it is fused with cementum.

34. Which one of the following substances is synthesized in the pituitary gland?

(A) Oxytocin
(B) Antidiuretic hormone
(C) Somatotropin
(D) Neurophysin
(E) Vasopressin

35. Which one of the following is true in breast cancer cells that involve the *BRCA1* gene?

(A) Mutated cells are unable to divide because of increased expression of the *BRCA1* gene.
(B) Mutated cells fail to reach the G_1–S checkpoint.
(C) Mutated cells have an abnormal number of endosomes.
(D) Mutated cells lose their G_2–M cell cycle checkpoint.
(E) Mutated cells become haploid because of the interaction of the *BRCA1* and *p53* genes.

Questions 36 to 38 refer to the following clinical scenario.

A 42-year-old man arrives in the emergency department with a rash over much of his face, hands, and arms. He states that he was gardening and pulled out a number of weeds. On questioning the patient, the physician realized that the patient inadvertently came in contact with poison ivy.

36. Which of the following cells is responsible for the release of the pharmacologic agents that caused the rash?

(A) DNES cells
(B) Myofibroblasts
(C) Mast cells
(D) Pericytes
(E) Plasma cells

37. Which of the following is a secondary mediator produced by the cell in Question 36?

(A) Histamine
(B) Chondroitin sulfate
(C) Neutral protease
(D) Bradykinin
(E) Aryl sulfatase

38. Which of the following white blood cells can also participate in the reaction of this patient to poison ivy?

(A) T cells
(B) B cells
(C) Neutrophils
(D) Basophils
(E) Eosinophils

39. A 26-year-old woman goes to the dentist because of a toothache. On examination, the dentist notes that the patient has a carious lesion that involves not only the enamel but also the dentin and the cementum of the tooth. Which of these substances cannot repair itself?

(A) Dentin
(B) Enamel
(C) Cementum
(D) Dentin and cementum
(E) Dentin, cementum, and enamel

40. Lisa is small and thin in stature. She spends her days indoors and rarely eats dairy products. When she became pregnant at 25 years of age, she had severe lower back and leg pain and tenderness when pressure was applied over bony regions of her body. Radiographs revealed excessive amounts of poorly mineralized osteoid in both femurs. Beneficial treatment of her condition involved high doses of vitamin D, calcium, and phosphorus, a regimen that continued after successful delivery of her baby. Which of the following describes Lisa's disease?

(A) Osteogenesis imperfecta
(B) Osteoporosis
(C) Osteomalacia
(D) Osteopetrosis
(E) Osteopenia

41. Michael had visual problems within a day after being hit in the head with a ball during a soccer game. He saw large floaters and noticed that a dark film was blocking part of the vision in his right eye. An examination by an ophthalmologist revealed that he had a detached retina, and emergency surgery was done to save the vision in that eye. Which of the following retinal layers were separated from one another to cause Michael's condition?

(A) Layer 1 from layer 2
(B) Layer 2 from layer 3
(C) Layer 3 from layer 4
(D) Layer 5 from layer 6
(E) Layer 6 from layer 7

42. Blood coagulation entails a cascade of reactions that occur in two interrelated pathways, the extrinsic and intrinsic. All of the following are associated with the intrinsic pathway of blood coagulation *except*

(A) conversion of fibrinogen to fibrin.
(B) platelet aggregation.
(C) release of tissue thromboplastin.
(D) von Willebrand factor.
(E) calcium.

43. A scientist spent a summer in a remote region of Africa, where he studied exotic plants. On returning to the United States, he developed a cough and fever that would not go away. Laboratory tests revealed that he had contracted a roundworm, *Ascaris lumbricoides*. Which of the following cells would be expected to be significantly elevated in a differential count of his blood?

(A) Erythrocytes
(B) Lymphocytes
(C) Monocytes
(D) Eosinophils
(E) Neutrophils

44. A 45-year-old musician who played guitar for 26 years in a rock band noticed he was having difficulty hearing. An otolaryngologist confirmed his loss of hearing and associated it with prolonged exposure to loud sounds. Which of the following structures would show degenerative changes that would account for this man's hearing loss?

(A) Epithelium lining the inner portion of the tympanic membrane
(B) Hair cells in the ampullae of the semicircular ducts
(C) The auditory (eustachian) tube extending to the middle ear cavity
(D) Endfeet of the auditory neurons
(E) Ossicles in the middle ear

45. Which of the following is a protein circulating in the blood that functions in wound healing?

(A) Chondronectin
(B) Plasma fibronectin
(C) Osteonectin
(D) Matrix fibronectin
(E) Laminin

46. Which of the following is an adhesive glycoprotein that forms fibrils in the extracellular matrix?

(A) Chondronectin
(B) Plasma fibronectin
(C) Osteonectin
(D) Matrix fibronectin
(E) Laminin

47. Which of the following is a multifunctional protein that attaches chondrocytes to type II collagen?

(A) Laminin
(B) Plasma fibronectin
(C) Osteonectin
(D) Matrix fibronectin
(E) Chondronectin

48. A patient exposed to an antigen produces antibodies against it. Which cell is responsible for the manufacture of the antibodies?

(A) Pericytes
(B) Macrophages
(C) T lymphocytes
(D) Plasma cells
(E) Mast cells

49. Principal phagocytes of connective tissue are the

(A) pericytes.
(B) macrophages.
(C) T lymphocytes.
(D) plasma cells.
(E) mast cells.

50. A patient who is experiencing an immediate hypersensitivity reaction is producing pharmacologic agents that are responsible for the reaction. Which cell manufactures those pharmacologic agents?

(A) Pericytes
(B) Macrophages
(C) T lymphocytes
(D) Plasma cells
(E) Mast cells

51. Which cells are responsible for the cell-mediated immune response experienced by the patient?

(A) Pericytes
(B) Macrophages
(C) T lymphocytes
(D) Plasma cells
(E) Mast cells

52. A patient who just arrived from a developing, land-locked, country known for inadequate amounts of iodine in the diet is prone to which one of the following conditions?

(A) Simple goiter
(B) Exophthalmic goiter
(C) Graves disease
(D) Addison disease
(E) Hyperparathyroidism

53. A patient whose adrenal cortex has been destroyed has which of the following conditions?

(A) Simple goiter
(B) Exophthalmic goiter
(C) Graves disease
(D) Addison disease
(E) Hyperparathyroidism

54. Which of the following is a rare form of skin cancer that may be fatal?

(A) Epidermolysis bullosa
(B) Basal cell carcinoma
(C) Malignant melanoma
(D) Psoriasis
(E) Warts

55. Which of the following is a hereditary skin disease characterized by blister formation after minor trauma?

(A) Epidermolysis bullosa
(B) Basal cell carcinoma
(C) Malignant melanoma
(D) Psoriasis
(E) Warts

56. Which of the following regions of the respiratory system would concern a patient with an adenoid?

(A) Trachea
(B) Nasopharynx
(C) Terminal bronchiole
(D) Alveolar duct
(E) Intrapulmonary bronchi

57. Which of the following is associated with rupture of the oviduct and hemorrhaging into the peritoneal cavity?

(A) Endometriosis
(B) Cervical cancer
(C) Ectopic tubal pregnancy
(D) Breast cancer
(E) Teratomas

58. Which of the following may be classified as lobular carcinoma?

(A) Endometriosis
(B) Cervical cancer
(C) Ectopic tubal pregnancy
(D) Breast cancer
(E) Teratomas

59. Which of the following may be detected by a Papanicolaou smear?

(A) Endometriosis
(B) Cervical cancer
(C) Ectopic tubal pregnancy
(D) Breast cancer
(E) Teratoma

60. Which of the following commonly results in hemorrhaging into the peritoneal cavity dependent on the stage of the menstrual cycle?

(A) Endometriosis
(B) Cervical cancer
(C) Ectopic tubal pregnancy
(D) Breast cancer
(E) Teratoma

61. Which of the following facilitates the absorption of vitamin B_{12}?

(A) Pepsin
(B) Enzyme associated with the glycocalyx of the intestinal striated border
(C) Lipase
(D) Chylomicron
(E) Gastric intrinsic factor (GIF)

62. A patient who was born with a mutation in the gene that results in the formation of defective chloride channels has which of the following conditions?

(A) Multiple sclerosis
(B) Cystinuria
(C) Cystic fibrosis
(D) Osteomalacia
(E) Hirschsprung disease

63. An individual with cholera is infected by *Vibrio cholerae* carrying a toxin that acts on which G protein?

(A) Inhibitory G protein (G_i)
(B) Phospholipase C activator G protein (G_q)
(C) Olfactory-specific G protein (G_{olf})
(D) Stimulatory G protein (G_s)
(E) Transducin (G_t)

64. Neurons responsible for limb movement of a patient afflicted by hereditary spastic paraplegia do not myelinate their axons completely, resulting in spastic limb movement. This condition appears to be due to the formation of abnormal scaffolding proteins that interfere with the normal assembly of

(A) mitochondria.
(B) endoplasmic reticulum (ER).
(C) lysosomes.
(D) endosomes.
(E) peroxisomes.

65. Most patients with Leigh disease die in their first year of life, although some individuals may reach 10 years of age. This inherited condition affects the proper functioning of which of the following organelles?

(A) Mitochondria
(B) Nuclear pore complex
(C) Ribosomes
(D) Endosomes
(E) Golgi apparatus

66. Babies who are born with Zellweger syndrome have a very short lifespan because of severe neurologic, liver, and kidney malfunctions. The organelles responsible for this disease are the

(A) mitochondria.
(B) Golgi complex.
(C) lysosomes.
(D) proteasomes.
(E) peroxisomes.

67. A 42-year-old female patient, who presents with mood disorders, loss of muscular coordination, and involuntary, erratic movements is diagnosed with Huntington disease. The condition is due to mutations in the *Huntingtin (HTT) genes*. Which of the following structures is affected in this disease?

(A) Mitochondria
(B) Nuclear pore complex
(C) Ribosomes
(D) Endosomes
(E) Golgi apparatus

68. A patient with aneuploidy whose karyotype is XXY has a condition known as

(A) Down syndrome.
(B) Turner syndrome.
(C) Klinefelter syndrome.
(D) Angelman syndrome.
(E) Prader–Willi syndrome.

69. A patient suffering from pernicious anemia has a severe deficiency of which vitamin?

(A) B_2
(B) B_5
(C) B_6
(D) B_9
(E) B_{12}

70. The coagulation disorder in which the patient has a deficiency in factor VIII is known as

(A) von Willebrand disease.
(B) hemophilia A.
(C) Glanzmann thrombasthenia.
(D) thrombocytopenia.
(E) Bernard–Soulier syndrome.

71. A patient whose symptoms are fatigue; irritability; patches of discolored skin with brittle, corkscrew-shaped hair; joint pain; bleeding gums; and tooth loss associated with poorly hydroxylated tropocollagen is suffering from

(A) deficiency of vitamin B_2.
(B) excess of vitamin B_2.

(C) deficiency of vitamin C.
(D) excess of vitamin C.
(E) excess of vitamin A.

72. A male patient, who has hearing disorders and an anomaly of the lens of his eyes known as lenticonus, has also been shown to have glomerulonephritis. This patient has a genetic defect known as Alport syndrome. Which collagen fiber type is affected by this condition?

(A) Type I
(B) Type II
(C) Type IV
(D) Type VII
(E) Type XII

73. Charcot–Marie–Tooth disease is an inherited condition that affects the myelin sheath, resulting in degeneration of the affected nerve and atrophy of the muscles served by those nerves because of a mutated gene. Most of the muscles affected initially are those of the lower limbs, and the patient exhibits walking difficulties, tripping, stumbling, and falling. Many of the affected individuals show evidence of an unusual gait, lifting their feet higher than necessary. Their lower leg muscles show signs of atrophy. This mutation affects which of the following?

(A) Zonula occludens
(B) Zonula adherens
(C) Desmosomes
(D) Hemidesmosomes
(E) Gap junctions

74. A 43-year-old male patient complains of pain in the back and sides as well as headaches and is diagnosed with the genetic disorder, caused by mutations in the *polycystic kidney disease-1 (PKD-1)* gene, that results in PKD. These individuals develop abnormal

(A) primary centrioles.
(B) primary cilia.
(C) cilia.
(D) microvilli.
(E) flagella.

75. A female patient with Barrett epithelium has a glandular mucus-secreting epithelium in her

(A) vagina.
(B) uterus.
(C) urinary bladder.
(D) esophagus.
(E) stomach.

76. What is the diagnosis for an adult male patient whose complete blood count had the following number of cells/mm^3: erythrocytes = 5×10^6, lymphocytes = 2,000, monocytes = 600, neutrophils = 5,000, eosinophils = 950, basophils = 75, platelets = 350,000?

(A) Eosinophilia
(B) Thrombocytopenia
(C) Lymphocytopenia
(D) Anemia
(E) Chronic leukemia

77. During the winter semester, a young male freshman college student goes to the infirmary complaining about weakness; muscle pains; nausea; vomiting; and, occasionally, confusion. The urine sample he produced was darker than normal, and the lab result indicated myoglobinuria. The patient had no hearing loss or breathing problems and had a normal heart rhythm. What does the examining physician suspect?

(A) Rhabdomyosarcoma
(B) Ethanol myopathy
(C) Desmin-related myopathy
(D) Growing pains
(E) Facioscapulohumeral muscular dystrophy

78. A young male patient who has enlarged lymph nodes, spleen, and liver complains of weight loss and weakness and is running a fever. Biopsy of his lymph node displays the presence of Reed–Sternberg cells. What condition should the physician suspect?

(A) Variable immunodeficiency
(B) DiGeorge syndrome
(C) Leukemia
(D) Non-Hodgkin disease
(E) Hodgkin disease

79. A long-term female smoker was diagnosed with lung cancer. Her physician told her that this type of lung cancer has the best prognosis. What type of lung cancer does she have?

(A) Large cell carcinoma
(B) Small cell carcinoma
(C) Squamous cell carcinoma
(D) Adenocarcinoma
(E) Oat cell carcinoma

80. Inhibition of α_1-antitrypsin is responsible for a respiratory condition known as

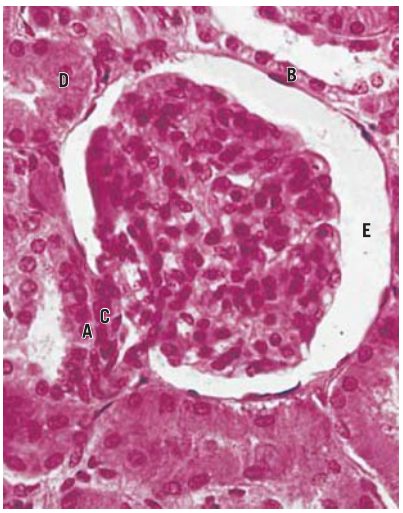
(A) hypersensitive pneumonitis.
(B) bronchitis.

(C) hyaline membrane disease.
(D) asthma.
(E) emphysema.

81. A painful condition of the oral region has three possible timings of the occurrence of the symptoms. Type 1 starts with no pain when the patient wakes up, but the pain increases as the day progresses; type 2 starts with pain upon awakening and continues throughout the day; and, in, type 3, the pain appears randomly. What is the name of the condition?

(A) Oral cancer
(B) Burning mouth syndrome (BMS)
(C) Angular cheilitis
(D) Herpetic stomatitis
(E) Canker sore

Questions 82 to 85 refer to the photomicrograph below.



82. The structure where proteins are resorbed is denoted by which letter?

(A) A
(B) B
(C) C
(D) D
(E) E

83. The structure that synthesizes and releases the enzyme that converts angiotensinogen to angiotensin I is denoted by which letter?

(A) A
(B) B
(C) C
(D) D
(E) E

84. The structure in which glucose is resorbed is denoted by which letter?

(A) A
(B) B
(C) C
(D) D
(E) E

85. The hormone aldosterone acts on the cells of the structure denoted by which letter?

(A) A
(B) B
(C) C
(D) D
(E) E

Answers and Explanations

1. **C.** To yield mRNPs, introns are excised, whereas exons are spliced together. DNA does act as the template for the synthesis of RNA. Three RNA polymerases (I, II, and III) are needed to synthesize ribosomal RNA, messenger RNA, and transfer RNA, respectively. Protein moieties are removed from the mRNPs as they leave the nucleus to yield functional mRNAs outside the nucleus.
2. **C.** The most common cause of osteoporosis in older women is diminished estrogen secretion.
3. **E.** Although adenine, cytosine, and guanine are found in both DNA and RNA, uracil is found only in RNA. Uracil substitutes for the base thymine in DNA.
4. **A.** Pancreatic centroacinar cells form the initial segment of the intercalated duct and are part of the exocrine pancreas. They secrete an enzyme-poor alkaline fluid when stimulated by secretin. Pancreatic digestive enzymes are synthesized by the acinar cells of the exocrine pancreas; their release is stimulated by cholecystokinin. Glucagon is produced in the endocrine pancreas (islets of Langerhans).
5. **E.** The zona fasciculata, the largest region of the adrenal cortex, produces glucocorticoids (cortisol and corticosterone). The zona glomerulosa produces mineralocorticoids, primarily aldosterone. Epinephrine is produced in the adrenal medulla. Glucagon is produced in the pancreas, not in the adrenal gland.
6. **B.** Diarthroses, the type of joint connecting two long bones, are classified as synovial joints, which are surrounded by a two-layered capsule housing a synovial membrane. Type A cells of the synovial membrane are phagocytic, whereas type B cells secrete the synovial fluid. Synarthrosis joints are those found joining the bones of the skull, which are immovable.
7. **E.** Neutrophils have a nucleus with three or four lobes, many azurophilic granules, and small specific granules that lack peroxidase. In contrast, basophils have an S-shaped nucleus, few azurophilic granules, and large specific granules that contain peroxidase. Both neutrophils and basophils possess mitochondria.
8. **D.** Oral leukoplakia, which results from epithelial hyperkeratosis, is usually of unknown etiology but often is associated with the use of chewing tobacco. Although the characteristic painless lesions are benign, they may transform into squamous cell carcinoma. Aphthous ulcers are painful lesions of the oral mucosa that are surrounded by a red border. Adenocarcinoma is a form of cancer arising in glandular tissue. Keloids are swellings in the skin that arise from increased collagen formation in hyperplastic scar tissue. Epidermolysis bullosa is a group of hereditary skin diseases characterized by blister formation after minor trauma.
9. **B.** A primordial follicle is composed of a flattened layer of follicular cells surrounding a primary oocyte, which is arrested in prophase of meiosis I. Well-defined thecal layers and a thick zona pellucida are found in growing follicles. A Graafian (mature) follicle possesses a secondary oocyte, which becomes arrested in metaphase of meiosis II just before ovulation.
10. **E.** The vestibular membrane belongs to the organ of Corti, which is responsible for the auditory function of the inner ear, whereas the other structures belong to that part of the inner ear that is responsible for vestibular function.
11. **D.** Euchromatin, the transcriptionally active form of chromatin, represents only about 10% of the chromatin. In the light microscope, it appears as a light-staining, dispersed region of the nucleus.
12. **C.** Large protein molecules cannot move across intercalated disks (the steplike junctional complexes present in cardiac, not smooth, muscle). These junctional structures possess three specializations: desmosomes, which provide end-to-end attachment of cardiac muscle cells; fasciae adherentes, to which the thin myofilaments attach; and gap junctions, which permit intercellular movement of small molecules and ions (ionic coupling).

13. D. Flattened squamous cells are characteristic of an unstimulated, inactive thyroid gland. TSH binds to G protein–linked receptors on the basal surface of follicular cells. Under TSH stimulation, thyroid follicular cells become columnar and form pseudopods, which engulf colloid. Lysosomal enzymes split thyroxine and triiodothyronine from thyroglobulin; the hormones are then released basally.

14. D. The enamel organ is epithelially derived, whereas the dental papilla comes from ectomesenchyme. The bell, not the cap, stage of odontogenesis is characterized by possessing a fourth layer in its enamel organ. Formation of dentin and enamel occurs during the appositional stage of tooth development. Cementum is located on the root and is formed only after the crown is complete and enamel ceases to be elaborated.

15. D. Liver sinusoids convey blood to the central vein. Their endothelial cells are fenestrated, and material from the sinusoids may enter the space of Disse through the fenestrae, where it may be endocytosed by hepatocytes. The space of Disse houses Ito cells (fat-storing cells). Because bile is the exocrine secretion of hepatocytes, it does not enter the sinusoids.

16. D. The toxin from *C. botulinum* inhibits the release of acetylcholine, the neurotransmitter at myoneural junctions. As a result, motor nerve impulses cannot be transmitted across the junction, and muscle cells are not stimulated to contract.

17. A. The nucleosome, the structural unit of chromatin packing, does not contain RNA. In extended chromatin, two copies each of histones H2A, H2B, H3, and H4 form the nucleosome core around which a DNA molecule is wound. Condensed chromatin contains additional histones (H1), which bind to nucleosomes, forming the condensed 30-nm chromatin fiber.

18. C. Only infectious mononucleosis is characterized by all of the signs and symptoms indicated. AIDS is associated with a decreased lymphocyte count, particularly of T helper cells. Pernicious anemia is associated with a decreased red blood cell count. Hodgkin disease is associated with fatigue and enlarged lymph nodes, but the nodes are not painful, and the presence of Reed–Sternberg cells is diagnostic of this disease. Factor VIII deficiency, a coagulation disorder, is not associated with any of these signs and symptoms.

19. C. The gallbladder, which concentrates and stores bile, is lined by a simple columnar epithelium. Cholecystokinin stimulates contraction of the gallbladder wall, forcing bile from the lumen into the cystic duct; this joins the common hepatic duct to form the common bile duct, which delivers bile to the duodenum.

20. A. Uncoupling of oxidation from phosphorylation induces mitochondria to change from the orthodox to the condensed form. Condensed mitochondria are often present in brown fat cells, which produce heat rather than adenosine triphosphate. Mitochondria possess circular DNA, and they reproduce (divide) by fission.

21. D. Muscular (distributing) arteries have a thick, complete internal elastic lamina in the tunica intima, whereas elastic (conducting) arteries have an incomplete internal elastic lamina. Both types of arteries have vasa vasorum, factor VIII, and smooth muscle cells in their walls. Muscular arteries possess numerous layers of muscle cells in the tunica media, but elastic arteries do not. Only elastic arteries possess fenestrated (elastic) membranes in the tunica media, in which smooth muscle cells are dispersed.

22. C. In the endocrine pancreas, β cells account for about 70% of the secretory cells, α cells about 20%, and δ cells less than 5%. Polypeptide hormones are synthesized by and released from the islets of Langerhans (endocrine pancreas). The exocrine pancreas possesses serous (not mucous) acinar cells. Insulin is produced by β cells.

23. B. Somatostatin and urogastrone both inhibit the production of hydrochloric acid, whereas gastrin enhances it. Secretin and cholecystokinin act on the pancreas to facilitate secretion of buffer and pancreatic enzymes, respectively.

24. A. A deficiency of vitamin A inhibits bone formation and growth, whereas an excess stimulates ossification of the epiphyseal plates, thus leading to premature closure of the plates. Both conditions result in short stature. A deficiency of vitamin D reduces calcium absorption from the small intestine and results in soft bones, whereas an excess of vitamin D stimulates bone resorption. A

deficiency of vitamin C results in poor bone growth and fracture repair. Vitamin K plays no role in bone formation.

25. **C.** Membrane-coating granules are present in keratinocytes in the stratum spinosum (and stratum granulosum). The contents of these granules are released into the intercellular spaces to help waterproof the skin. Keratinocytes in the stratum granulosum also possess keratohyalin granules; these contain proteins that bind keratin filaments together.

26. **A.** The nucleus of erythroblasts is not in the process of being extruded and is round with a very fine chromatin network. The cytoplasm is blue and possesses no granules.

27. **B.** The ileum includes Peyer patches. Rugae, parietal cells, and chief cells are located in the stomach. Brunner glands are present in the submucosa of the duodenum.

28. **B.** Herpetic stomatitis is characterized by painful fever blisters on the lips or near the nostrils. These blisters exude a clear fluid. Aphthous ulcers (canker sores) do not exude fluid. Bullous pemphigoid is an autoimmune disease marked by chronic generalized blisters in the skin.

29. **C.** The skin, which consists of the epidermis and dermis, is important in the regulation of body temperature and contains temperature receptors in the dermis. Ultraviolet (not infrared) radiation absorbed by the skin is necessary for the synthesis of vitamin D. Protection against desiccation is provided by the contents of the membrane-coating granules of the epidermis. Melanocytes are located in the deepest layer of the epidermis (stratum basale). Sunscreen with sun protection factor rating of 15 or higher offers no protection against ultraviolet light of longer wavelengths, that is, in the UVA spectrum.

30. **C.** Patients with glomerulonephritis excrete protein in their urine. All of the other symptoms are characteristic of patients with diabetes insipidus, who are incapable of producing adequate amounts of antidiuretic hormone and therefore have polyuria (large volume of hypotonic urine production), polydipsia, and dehydration.

31. **E.** The anus is lined by stratified squamous keratinized epithelium. The rectum, jejunum, and pylorus are lined by simple columnar epithelium. The esophagus is lined by stratified squamous (nonkeratinized) epithelium.

32. **C.** Hyaline membrane disease, which results from inadequate amounts of pulmonary surfactant, is characterized by labored breathing and is typically observed in premature infants. Glucocorticoids stimulate synthesis of surfactant and can correct the condition.

33. **A.** The cribriform plate, the inner layer of the alveolar bone, is composed of compact bone. It is attached to the principal fiber groups of the periodontal ligament via Sharpey fibers. The outer layer of the alveolar bone is the cortical plate. The spongiosa is the region of cancellous (spongy) bone enclosed between the cortical and cribriform plates.

34. **C.** Somatotropin (growth hormone) is synthesized by cells called somatotrophs, which are acidophils located in the pars distalis of the anterior lobe of the pituitary gland. Oxytocin and antidiuretic hormone (also called vasopressin) are produced in the hypothalamus and transported to the pars nervosa of the pituitary. Neurophysin, a binding protein, aids in this transport.

35. **D.** Mutations in the *BRCA1* gene, a breast tumor–suppressor gene, are the major cause of breast cancer. In most breast cancers involving this gene, DNA synthesis proceeds, indicating that the G_1–S checkpoint is not affected; however, the mutated cells cannot control the transition between G_2 and M. Moreover, the mutated cells had abnormal centrosome numbers and their nuclear division did not proceed normally, leading to aneuploidy and genetic instability of the daughter cells.

36. **C.** The patient has an immediate (type I) hypersensitivity reaction. The cells responsible for releasing the primary and secondary mediators are the mast cells.

37. **D.** Bradykinins are the only listed pharmacologic agents that are produced via the arachidonic acid pathway. All of the others are primary mediators because they are stored in the storage granules of mast cells.

38. **D.** Basophils are very similar in function to mast cells. They also participate in the immediate (type I) hypersensitivity reaction.

39. B. The only hard tissue of the tooth that cannot be repaired by the body is enamel because ameloblasts, the cells that manufacture enamel, are eliminated as the tooth emerges into the oral cavity.

40. C. Osteomalacia, or adult rickets, is Lisa's disorder. It is characterized by a failure of newly formed osteoid to calcify because of a lack of calcium, vitamin D, and phosphorus. The bones gradually soften and bend, and pain accompanies the condition, which often becomes severe during pregnancy as the fetus removes calcium from the mother's body. Osteogenesis imperfecta is a genetic condition affecting the synthesis of type I collagen in the bone matrix and results in extreme bone fragility and breakage. Osteoporosis is a disease characterized by low bone mineral density and structural deterioration, making bone more susceptible to fracture, and osteopenia is reduced bone mass caused by inadequate osteoid synthesis. Osteopetrosis is the excessive formation of bone, which obliterates the marrow cavities and thus impairs the formation of blood cells.

41. A. The pigmented epithelium (layer 1) was separated from the layer of rods and cones (layer 2), which make up the light-sensitive part of the neural retina.

42. C. The extrinsic pathway is initiated by the release of tissue thromboplastin after trauma to extravascular tissue. Platelet aggregation is promoted by von Willebrand factor, which is associated with the intrinsic pathway only. Calcium is required in both pathways, and the final reaction—the conversion of fibrinogen to fibrin—is the same in both.

43. D. Eosinophils are increased in parasitic infections and allergic reactions. Both eosinophils and basophils have receptors for immunoglobulin E, which seems to be important in the destruction of parasites. Both neutrophils and monocytes lack immunoglobulin E receptors.

44. D. The inner ear is where sound waves are transduced into nerve impulses that convey auditory information to the brain, and the endfeet of auditory neurons synapsing with the hair cells of the organ of Corti play a key role in this process. Hair cells are quite sturdy, whereas the endfeet of the unipolar (formerly known as pseudounipolar) auditory neurons are easily damaged.

45. B. Plasma fibronectin functions in wound healing, blood clotting, and phagocytosis of material from the blood.

46. D. Matrix fibronectin mediates cell adhesion to the extracellular matrix by binding to fibronectin receptors on the plasma membrane.

47. E. Chondronectin has binding sites for type II collagen, proteoglycans, and chondrocyte cell surface receptors.

48. D. Plasma cells, which arise from antigen-activated B lymphocytes, produce antibodies and thus are directly responsible for humoral-mediated immunity.

49. B. Macrophages, the principal phagocytes of connective tissue, remove large particulate matter and assist in the immune response by acting as antigen-presenting cells.

50. E. Mast cells (and basophils) have receptors for immunoglobulin E antibodies on their surface. These cells release histamine, heparin, leukotriene C (slow-reacting substance of anaphylaxis), and eosinophil chemotactic factor, which have effects that constitute immediate hypersensitivity reactions.

51. C. T lymphocytes initiate cell-mediated immune responses.

52. A. Simple goiter is an enlargement of the thyroid gland resulting from inadequate dietary iodine (less than 10 μg/d). It is common where the food supply is low in iodine.

53. D. Addison disease is most commonly caused by an autoimmunity that destroys the adrenal cortex. As a result, inadequate amounts of glucocorticoids and mineralocorticoids are produced. Unless these are replaced by steroid therapy, the disease is fatal.

54. C. Malignant melanoma, a relatively rare form of skin cancer, arises from melanocytes. It is aggressive and invasive. Surgery and chemotherapy usually are necessary for successful treatment of this cancer.

55. A. Epidermolysis bullosa is a group of hereditary skin diseases characterized by the separation of the layers in skin with consequent blister formation.

56. B. The nasopharynx is the site of the pharyngeal tonsil; when enlarged and infected, this tonsil is known as an adenoid.

57. C. An ectopic tubal pregnancy occurs when the embryo implants in the wall of the oviduct (rather than in the uterus). Because the oviduct cannot support the developing embryo, the duct eventually bursts, causing hemorrhaging into the peritoneal cavity.

58. D. Breast cancer that originates from the epithelium lining the terminal ductules of the mammary gland is classified as lobular carcinoma.

59. B. Abnormal cells associated with cervical cancer are revealed in a Papanicolaou (Pap) smear, providing a simple method for the early detection of this cancer.

60. A. Endometriosis is a condition in which uterine endometrial tissue is located in the pelvic peritoneal cavity. The misplaced endometrial tissue undergoes cyclic hormone-induced changes, including menstrual breakdown and bleeding.

61. E. GIF, which is produced by parietal cells in the gastric glands, is necessary for absorption of vitamin B_{12} in the ileum.

62. C. Cystic fibrosis is a hereditary disease involving a mutation in the cystic fibrosis transmembrane conductance regulator gene (*CFTR* gene) that causes the manufacture of malformed chloride channel proteins that are unable to transport chloride ions, causing an increase in the entry of Na^+ ions into the cell. The higher intracellular concentration of NaCl causes the increased flow of water into the cell, and the mucin that is released into the extracellular environment cannot become normally hydrated, thus making the mucus thicker than normal, which obstructs the very small bronchiolar passageways of the lungs. As the disease progresses, infections result, the lungs become unable to function properly, and the individual succumbs to the disease and dies.

63. D. Cholera toxin is an exotoxin produced by the bacterium *V. cholerae* that alters G_s protein so that it is unable to hydrolyze its guanosine triphosphate molecule. As a result, cyclic adenosine monophosphate levels increase in the surface-absorptive cells of the intestine, leading to excessive loss of electrolytes and water and severe diarrhea.

64. B. Mutations in the ER-shaping proteins may have serious clinical consequences. Some of these altered proteins are responsible for a condition known as hereditary spastic paraplegia that affects some of the neurons responsible for limb movement. The absence of normal scaffolding protein prevents the ER tubules from forming three-way junctions with each other, thereby interfering with the ability of the ER to form lipids, resulting in abnormal lipid metabolism and myelin formation. The reduction in myelin in the axons of the primary motor neurons results in spastic limb movements.

65. A. Leigh disease is due to mutations either in the mitochondrial DNA itself or in the nuclear DNA that codes for mitochondrial proteins. Although Leigh disease is rare, it is lethal within the first year or so of life and rarely does the affected individual reach 10 or more years. Most of the body's tissues that have a high energy requirement (skeletal and cardiac muscles; neurons) decline because the cells' mitochondria are unable to provide enough energy to maintain them in a healthy condition. Therefore, the muscular system, the heart, and many neurons progressively deteriorate. Most mitochondria of an affected individual seem to have malformations in one or more of the enzymes responsible for oxidative phosphorylation.

66. E. Zellweger syndrome is a genetic disease in which normal peroxisomes are absent. Infants with this syndrome have profound neurologic disorders and liver and kidney problems and usually die within a few months. Electron micrographs of biopsies from these patients reveal empty peroxisomes, lacking enzymes. Although peroxisomal enzymes may be synthesized, they become dislocated in the cytosol.

67. B. Mutations in the HTT genes are responsible for the inherited condition known as Huntington disease that affects 10 in 100,000 people of Caucasian descent; men and women are affected equally. The mutation affects nucleoporins that cause functional disturbances in the nuclear pore complexes, which become unable to permit the transport of proteins from the nucleus into the cytoplasm. The accumulated proteins in the nucleus interfere with the functions of the neuron, resulting in this debilitating, lethal condition.

68. C. Aneuploidy, defined as an abnormal number of chromosomes, can be detected by karyotyping. The karyotype XXY is known as Klinefelter syndrome.

69. E. Severe deficiency of the coenzyme vitamin B_{12} is responsible for the condition known as pernicious anemia. Usually, this condition is due to the impaired production of GIF by the parietal cells of the stomach. GIF is required for the proper absorption of vitamin B_{12} in the ileum.

70. B. Coagulation disorders frequently result from inherited or acquired defects of coagulation factors. Hemophilia A (factor VIII deficiency) is an X-linked disorder that affects mostly men, but, because men contribute a Y chromosome, they cannot pass the condition to their sons. However, they can contribute a defective X chromosome to their daughters who, then, become carriers. Only about 65% of the cases are due to inheritance and 35% are due to spontaneous mutations.

71. C. Deficiency of vitamin C, a cofactor with iron in hydroxylation of proline and lysine residues, causes scurvy, the synthesis of poorly hydroxylated tropocollagen, which is unable to form either a stable triple helix or collagen fibrils. The symptoms of scurvy include fatigue; irritability; patches of discolored skin with brittle, corkscrew-shaped hair; joint pain; bleeding gums; and eventual tooth loss.

72. C. Alport syndrome is the result of genetic defects in the genes that are responsible for the formation of collagen types III, IV, and V, which result in the abnormal type IV collagen assembly. Because the lamina densa of the basal lamina is formed mostly by type IV collagen, individuals afflicted by Alport syndrome present with glomerulonephritis that results in end-stage kidney disease. These individuals also have hearing disorders and an anomaly of the lens of their eyes known as lenticonus, a bulge that occurs in the lens during development; the consequence of the bulge may be a herniated lens.

73. E. Charcot–Marie–Tooth disease, an inherited condition, has been shown to be due to a mutation in the gene that codes for protein Cx32 of hemichannels (connexons) located in myelin sheaths. The progressive decrease in the number of gap junction channels results in the degradation of the myelin sheath, resulting in degeneration of the affected nerve and atrophy of the muscles served by those nerves. Fortunately, the condition is not fatal, and affected individuals have a normal life span.

74. B. PKD, a genetic disorder, is an autosomal dominant disease occurring in about 2 per 1,000 births. Three mutations are responsible for this anomaly, namely PKD-1, PKD-2, and PKHD-1, but most cases are due to mutations in gene PKD-1 located on chromosome 16. For an unknown reason, individuals with these mutations develop abnormal primary cilia, resulting in abnormal cell cycles as well as defective calcium transport within the cell. During embryonic development, cysts begin forming on the kidneys. These cysts progressively increase in size and number, and, as they continue to gain fluid and become larger, they apply pressure on the uriniferous tubules and prevent them from performing their function. In most patients, the symptoms, such as pain in the back and sides as well as headaches, become evident by the 40th year of life, and, eventually, the kidney function of the patients is reduced until they have to be placed on renal dialysis and become eligible for kidney transplant.

75. D. Most commonly, a glandular epithelium is transformed into a squamous epithelium. However, in cases of chronic acid reflux from the stomach into the lower esophagus, the stratified squamous nonkeratinized epithelium of the esophagus is replaced by a glandular mucus-secreting epithelium (Barrett epithelium) similar to that found lining the cardia of the stomach. This helps to protect the esophagus against the injurious effects of the acid and pepsin but is also a well-known precursor of esophageal adenocarcinoma.

76. A. This is a normal complete blood count for an adult male, except for the eosinophils that are much higher than normal; therefore, the diagnosis is eosinophilia.

77. B. Ethanol myopathy may occur as a result of binge drinking. This condition is characterized by destruction of skeletal muscle fibers (rhabdomyolysis) associated with myoglobinuria (myoglobin in the urine). In more severe cases, the patient frequently complains about weakness and pain of the affected muscles (or sometimes all muscles); nausea; vomiting; and, occasionally,

confusion and even the possibility of renal failure. The urine may also be darker than normal because of the released myoglobin. Muscle biopsies present with swollen, degenerating muscle cells and phagocytosis of damaged muscle fibers. Regeneration attempts by the muscle may also be evident. Growing pains are not accompanied by nausea, vomiting, muscle weakness, myoglobinuria, or confusion. Rhabdomyosarcoma occurs most often in young children and they form tumors. Desmin-related myopathy and facioscapulohumeral muscular dystrophy are accompanied by breathing problems and abnormal heart rhythm.

78. E. Hodgkin disease, a malignant neoplastic transformation of lymphocytes, occurs mostly in young men and is characterized by the presence of Reed–Sternberg cells, which are giant cells with two large, vacuolated nuclei, each with a dense nucleolus. Signs and symptoms of Hodgkin disease include painless progressive enlargement of the lymph nodes, spleen, and liver; anemia; fever; weakness; anorexia; and weight loss. None of the other conditions listed have Reed–Sternberg cells.

79. D. Adenocarcinomas account for about 40% of all lung cancers and are more common in women than in men. Most of the cases of adenocarcinoma are smoking related, but it frequently occurs in individuals who are nonsmokers. Of all the lung cancers, this has the best prognosis. Oat cell carcinoma is also known as small cell carcinoma.

80. E. Emphysema results from destruction of alveolar walls and formation of large cystlike sacs, reducing the surface area available for gas exchange. It is marked by decreased elasticity of the lungs, which are unable to recoil adequately during expiration. In time, the lungs expand and enlarge the thoracic cavity (barrel chest). Emphysema is associated with exposure to cigarette smoke and other substances that inhibit α_1-antitrypsin, a protein that normally protects the lungs from the action of elastase produced by alveolar macrophages. However, it can be a hereditary condition resulting from a defective α_1-antitrypsin. In such cases, gene therapy with recombinant α_1-antitrypsin is being used in an effort to correct the problem, and it has recently been successful in boosting the availability of this protective protein.

81. B. BMS is a painful condition in which the patient has a burning sensation of the mouth and/or tongue. In some individuals, the sensation is more of numbness than of burning. Frequently, the condition is accompanied by an altered taste sensation, such as a metallic taste or a bitter taste of inexplicable origin. In some patients, dryness in the mouth due to lessened saliva production is also present. The cause of BMS is not known, although some researchers suggest that the patient is suffering from vitamin B_{12} deficiency, candidiasis, acid influx, certain prescription medications, allergies, the use of dentures, and even depression and anxiety. The condition is more common in women than in men. The three types of BMS depend on the timing of the presence of symptoms: Type 1 presents with no symptoms at awakening, and the pain increases as the day progresses; in type 2, the burning sensation is present as the patient wakes up and continues as the day progresses; and, in type 3, the symptoms appear in a random fashion.

82. D. Proteins, in this photomicrograph, are resorbed by cells of the proximal convoluted tubule, indicated by the letter D.

83. C. The enzyme, renin, which transforms angiotensinogen to angiotensin I, is synthesized and secreted by the juxtaglomerular cells, indicated by the letter C.

84. D. Glucose, in this photomicrograph, is resorbed by cells of the proximal convoluted tubule, indicated by the letter D.

85. B. The hormone aldosterone, synthesized and released by cells of the suprarenal cortex, acts on the cells of the distal convoluted tubule, denoted by the letter B.

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